DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

January 30, 1989

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING[1]

January 30, 1989

The Recombinant DNA Advisory Committee (RAC) was convened for its fortieth meeting at 9:00 a.m. on January 30, 1989, in Building 31C, Conference Room 6, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. Gerard J. McGarrity (Chair), presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee members:

Candida R.T. Acosta	Robert P. Erickson	Gerald L. Musgrave
Ronald M. Atlas	Martin F. Gellert	Paul E. Neiman
Al W. Bourquin	Brian F. Mannix	Joseph S. Pagano
Michael F. Brewer	Robert D. McCreery	Monica Riley
Donald C. Carner	Gerard J. McGarrity	Jeffrey W. Roberts
James F. Childress	R. Scott McIvor	Moselio Schaechter
Don B. Clewell	Richard C. Mulligan	Anne K. Vidaver
Charles J. Epstein	Barbara E. Murray	Jay Moskowitz
	Robert F. Murray	(Executive Secretary)

A committee roster is attached (Attachment).

Ad hoc consultants:

Robert W. McKinney, National Institutes of Health
Sue A. Tolin, Department of Agriculture
LeRoy Walters, Kennedy Institute for Ethics
Anne R. Witherby

Liaison representative:

Daniel P. Jones, National Endowment for the Humanities

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[1]The RAC is advisory to the National Institutes of Health (NIH), and its recommendations should not be considered as final or accepted. The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Non-voting agency representatives:

Joel Dalrymple, Department of Defense
Phillip Harriman, National Science Foundation
Morris A. Levin, Environmental Protection Agency
Elizabeth A. Milewski, Environmental Protection Agency
Henry I. Miller, Food and Drug Administration
George P. Shibley, Department of Agriculture

National Institutes of Health staff:

W. French Anderson, NHLBI
Florence Antoine, NCI
Geraldine Blumberg, OD
Robert Crawford, OD
Calvin M. Foltz, NIDDK
Calvin Jackson, OD
Becky A. Lawson, OD
Rachel E. Levinson, OD
Melody Lind, OD
Michael Lotze, NCI
Kristin Olsen, OD
Alan Price, OD
Steven A. Rosenberg, NCI
Ann Stevens, NHLBI
Mary Sullivan, OD
Robert Weisberg, NICHD
Audrey Wright, NICHD
James B. Wyngaarden, OD

Others:

Elizabeth L. Anderson, Environmental Protection Agency
Stanley Barban
Manuel Barbeito, Department of Agriculture
Keith Belton, American Chemical Society
Janine Bertram, Endependence Center of Northern Virginia, Inc.
Arindam Bose, Pfizer
Robert Boyer, NBC
Dennis Brack, Time Magazine
Scott Bruns, NBC
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Chia Ting Chen, Occupational Safety and Health Administration
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I. CALL TO ORDER AND INTRODUCTORY REMARKS:

Dr. McGarrity, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) to order at 9:00 a.m., January 30, 1989. He said the meeting was called pursuant to a **Federal Register** notice which, being 30 or more days prior to today's date, met requirements of the **NIH Guidelines for Research Involving Recombinant DNA Molecules.** He stated that the meeting would remain open to the public for its entirety, and that he expected the meeting to conclude within one day.

Dr. McGarrity asked Dr. Moskowitz if a quorum was present and Dr. Moskowitz assured the Chair that a quorum was in attendance.

Dr. McGarrity noted that he intended to make every effort to abide by the distributed agenda with respect to time estimates for each item of business. He reminded the Committee that in recognizing persons for comments he would use the following order: primary and secondary reviewers on each item as set forth in the agenda; other members of RAC; ad hoc consultants to the RAC; NIH staff members; members of the public who had submitted written comments; and finally, other members of the public. He reminded participants that RAC was advisory to the Director of NIH, and in light of this, persons with minority opinions should voice them so as to provide Dr. Wyngaarden with the entire spectrum of opinions on a given topic. Dr. McGarrity then told the Committee that in all voting he would call first for the affirmative, then for the negative, and finally for abstentions. He emphasized that if any voting member felt compelled to abstain due to conflict of interest, the member should notify the Chair so that the record could duly reflect such situations.

Dr. McGarrity welcomed the following new members to the committee: Drs. Candida Acosta, Al Bourquin, Barbara Murray, and Moselio Schaechter. He noted that Dr. William Kelley of the University of Michigan Medical School had been appointed to the Committee but was unable to attend this meeting. He also welcomed Dr. Robert McKinney, Dr. Sue Tolin, Dr. LeRoy Walters and Ms. Anne Witherby who are serving as ad hoc advisors for this meeting.

Dr. McGarrity announced a change in the published agenda which resulted from a request by Mr. Jeremy Rifkin to address two agenda items dealing with amending the RAC Charter and the review of the public information brochure. This request was made in order to accommodate visitors representing associations for the handicapped and others who would be unable to attend the afternoon session. Dr. McGarrity thanked the Office of Recombinant DNA (ORDA) staff for being able to make these changes at the last moment.

II. APPROVAL OF THE MINUTES OF THE OCTOBER 3, 1988, MEETING:

Dr. McGarrity called on Dr. Neiman to present the minutes of the October 3, 1988, meeting. Dr. Neiman said he had read the minutes and found them to be clear, He had no comments or changes to recommend and moved their approval. Dr. Musgrave seconded the motion. Dr. McGarrity noted that if typographical errors or non-substantial changes were noted they could be brought to the attention of the staff.

Dr. McGarrity asked for further comment, and seeing none called for a vote on the motion. The motion to approve the minutes passed by unanimous vote.

III. HUMAN GENE THERAPY SUBCOMMITTEE STATUS REPORT:

Dr. McGarrity said he wished to bring the Committee up to date on the current status of the protocol brought forward by Drs. W. French Anderson, Steven A. Rosenberg and Michael R. Blaese to insert a neomycin-resistance gene into tumor-infiltrating lymphocytes (TIL) of cancer patients. He presented a brief history of the project as background, explaining that the experiment was not technically gene therapy, but rather gene insertion. He noted the Human Gene Therapy Subcommittee held several meetings, both in person and by conference call prior to the October 3, 1988 meeting of the Recombinant DNA Advisory Committee (RAC). At the time of that meeting, Subcommittee approval was being deferred pending receipt of additional data from the investigators.

Dr. McGarrity said this presented the RAC with an unusual situation in that the Committee was being asked to deliberate an issue before the Subcommittee had either approved or disapproved the protocol. The data requested by the Subcommittee was provided during the full committee meeting in October. In light of the fact that the gene transfer proposal had been published for comment as an agenda item in the **Federal Register** notice of the October meeting, its consideration by the full Committee was appropriate.

Dr. McGarrity noted that after the data had been presented at the RAC meeting in October, several Committee members said that although it looked convincing and scientifically sound, they would have preferred to have had more time to read and mull over the new information rather than having it presented in a brief fashion to the Committee. Dr. McGarrity noted that such concerns were not due to poor or insufficient data, but that some members desired more time for analysis.

Dr. McGarrity said the minutes of the October 3, 1988 RAC meeting reflected an overwhelming majority (16 in favor, 5 against) were in favor of approving the experiments to be performed under conditions as outlined in the meeting minutes.

Dr. McGarrity said he felt it was highly desirable, in view of the precedence of the studies, to give investigators who had some questions another chance to look at the data more closely, especially in light of the fact that some of those reviewers who requested more time to look at the data were members of the Human Gene Therapy

Subcommittee as well as the RAC. Therefore, the Human Gene Therapy Subcommittee met again on December 9, 1988. Following another presentation by the principal investigators, the Subcommittee voted unanimously (12 in favor, none opposed, no abstentions) to approve the proposal. However, Dr. McGarrity noted that the key point was that formal RAC recommendation for approval was given at the October 3, 1988 meeting.

Dr. McGarrity then called on Dr. James B. Wyngaarden, Director, National Institutes of Health, for his comments.

Dr. Wyngaarden said he wished to review the sequence of events that led up to his official acceptance of the recommendation of the RAC to approve the Anderson, Rosenberg, Blaese proposal on January 19, 1989, and said he believed the seven months of review was time very well spent in light of the importance of the issue.

Dr. Wyngaarden reiterated the history of the proposal from its receipt in June and July of 1988, by a number of NIH review committees charged with oversight of proposed experiments. He said one of the key elements in such reviews is the issue of safety; not only the safety of the patients involved in the studies, but also the safety of the investigators, other health care personnel, public health safety, and safety to the environment. He said the Institutional Review Boards (IRBs) of both the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI), as well as the NIH Institutional Biosafety Committee, all gave "conditional approval" with certain stipulations. Among the stipulations was a requirement for RAC approval of the proposed project.

Dr. Wyngaarden stated the Human Gene Therapy Subcommittee met on July 29, 1988, and deferred approval of the gene transfer proposal pending receipt of additional data. Subcommittee members prepared specific questions to be answered by the scientists prior to the October 3 RAC meeting. The Subcommittee met again via telephone conference on September 29, 1988, during which it was determined that the questions posed at the previous meeting still remained unanswered and they agreed again to defer approval of the proposal. On October 3, 1988, the RAC met and received data which had not been submitted previously to the Subcommittee. Based on the additional data presented, the Committee recommended approval of the protocol by a vote of 16 in favor and 5 against with no abstentions.

However, because certain questions raised by technical experts of the Human Gene Therapy Subcommittee had not yet been resolved, Dr. Wyngaarden reported that he requested the entire protocol, including data presented at the October 3 meeting and any additional data obtained, be reviewed by the Subcommittee at its December 9, 1988 meeting. He said this was done because of a strong belief that all data should come before all groups involved in the review of such an important matter and that the Government owes nothing less to the public.

Dr. Wyngaarden said he was aware of the need and desirability of conducting such business in public session and underlined the record of the RAC since 1974 in

announcing its meetings in the **Federal Register** as well as interacting with the news media to ensure the public is made aware of impending issues before the Committee.

Dr. Wyngaarden noted that the Human Gene Therapy Subcommittee did in fact review the additional data provided during the RAC meeting of October 3, 1988, and unanimously approved the protocol. He also noted that the two NIH IRBs had granted their approval, as had the NIH Institutional Biosafety Committee and the Vaccines and Related Biologics Products Advisory Committee of the Food and Drug Administration (FDA).

A mail ballot was then distributed to all RAC members that included the motion approved by the Human Gene Therapy Subcommittee and the minutes of the December 9, 1988 Subcommittee meeting. Because there had been no change in either the protocol or the motion previously approved by the RAC, Dr. Wyngaarden said he did not ask RAC members for further deliberation, but that the mail ballot was to provide a final formal record of the entire review process.

Dr. Wyngaarden said that the Human Gene Therapy Subcommittee had approved the same motion voted by the RAC at the October 3 meeting but had chosen to add a fourth point, a point of clarification, and thus the motion on the mail ballot was as follows:

> "To approve the human gene transfer proposal submitted by Drs. Anderson, Blaese, and Rosenberg with the following stipulations:
>
> "1. There will be no more than 10 patients in the initial trials;
>
> "2. The patients selected will have a life expectancy of about 90 days;
>
> "3. The patients give fully informed consent to participate in the trial; and
>
> "4. The investigators will provide additional data before expanding the trial by adding patients or by inserting a gene for therapeutic purposes.

In giving his approval, Dr. Wyngaarden added that, "throughout the process of review, the investigators have demonstrated to the satisfaction of the review committee that the use of amphotrophically packaged retroviral vectors does not appear to pose a public health risk to patients or to health care personnel, even in the event of accidental exposure to experimental material."

Dr. Wyngaarden said he had "accepted the recommendation brought before [him] and fully endorsed the start of this important, landmark research project. The detailed review procedure, the obvious expertise and commitment of the various members of the committees involved and the full and open discussion we have had convinced me

that this proposal and this protocol does not present a risk to public health or to the environment."

Dr. McGarrity then called on Dr. LeRoy Walters, Chairman of the Human Gene Therapy Subcommittee for his comments.

Dr. Walters said he was gratified by the long review process and by the attentiveness of everyone involved including the entire RAC membership. However, he felt after the October 3, 1988 meeting that there were two procedural issues which needed to be resolved for future review processes.

He said the first was, "whether all relevant data would be presented in written form to the relevant subcommittee and the parent RAC in advance of the meeting at which a proposal would be considered." He noted there were various reasons why this did not occur in the case of the Anderson, Blaese, Rosenberg proposal, but that the policy had been clarified on that point for future reviews.

The second point was, "whether the parent committee (RAC) will take up for formal action a proposal that has not received approval by the relevant subcommittee. He noted that an agenda item would be taken up later in this meeting relevant to that issue.

Dr. Walters called attention to the motion made at the meeting of the Subcommittee by Dr. Parkman which was that, "permission be given to initiate the [Anderson/ Blaese/Rosenberg] protocol providing the following 4 conditions are met:

"1. That the number of patients be limited to 10;

"2. That the patients have a life expectancy of about 90 days;

"3. That the patients give informed consent; and,

"4. That the investigators provide additional data before expanding the trial by adding patients or inserting a gene for therapeutic purposes."

Dr. Walters also noted a caveat to the motion provided by Dr. Murray who emphasized that "a clear statement must accompany this motion that approval does not constitute precedent for future experiments in gene therapy, particularly with respect to animal models." This wording was accepted as an amendment to the motion because the Subcommittee wanted to go on record as saying that if a therapeutic protocol were to come forward, they thought the requirements for an animal model system would need to be more stringent.

Dr. Walters thanked the RAC for the insights it provided in its October 3, 1988 meeting and for ratifying the Subcommittee recommendation via the mail ballot in December.

Dr. Mulligan said that "certainly from a scientific standpoint I think that we're very clear on the issues and I think we're happy at this point in time." He said the issue of procedures was one requiring further discussion.

There being no further comment from the committee, Dr. McGarrity called on Jeremy Rifkin, Foundation on Economic Trends, for his comments. Mr. Rifkin thanked the Committee for rearranging its schedule. He said he differed with the consensus arrived at by the Committee stating that many issues he originally brought to the Committee's attention in 1983 had not yet been addressed. In particular, he said the RAC had overridden the Subcommittee by agreeing to recommend approval of the protocol without prior approval by the Human Gene Therapy Subcommittee. Further, he said he had never before heard of a "mail vote" being taken by the RAC. In so doing, the RAC "undermined its own protocols," and breached the openness for which it had been known over the years. According to Mr. Rifkin, this action had prevented the public from being involved in the final deliberation process, thereby raising questions about future public interaction in the deliberations of the RAC.

Mr. Rifkin said two questions concerning this proposal had been raised by the RAC and needed to be assessed for public policy: (1) the fact that no animal model analogous to the human was available to provide data on which to judge the experiment; and (2) the value of the scientific data that would come out of the experiment was questionable because of the short life expectancy of the human experimental subjects. He said these two issues raised the concern that the human subjects of this research were being used as "guinea pigs" to "rush through a technological breakthrough which might not have any relevance in terms of the science of it."

Mr. Rifkin noted he had attended a meeting at the National Academy of Science in March, 1977, and had stated, "Eventually we're going to get to the point of human gene engineering, human gene therapy, and at that time we need a thorough public debate around the world about the value of introducing genes into human beings and rearranging the genetic code of somatic and germ line cells." He said there was tremendous resistance by some people who are on the RAC and in the room to entertain the larger eugenics and ethical questions of genetic engineering of human beings.

Mr. Rifkin said that in the 12 years since 1977, there had been no serious debate about the eugenics and ethical implications of gene engineering. He said it was true that the Committee had members who were qualified to discuss the medical benefits to the patient. However, he claimed that the larger issues of eugenics and ethics needed to be addressed at the beginning of human gene engineering as the likelihood of such debate would diminish as the technology progressed.

Mr. Rifkin then stated, "As a result of the indiscretions and the abuse of protocol of the Subcommittee and the full RAC in investigating this, and assessing and approving this first human gene experiment, our attorneys are filing a lawsuit in the U.S. District Court at 9:30 this morning to enjoin this first human gene experiment." He said his

organization would pursue a rigorous objection to the experiment via the courts until such time as the NIH and its advisory committees came into compliance with appropriate protocols to oversee human gene engineering.

Mr. Rifkin said this marked the beginning of a debate on the eugenics, ethical, and scientific merit of human gene engineering which would not allow for a "small fraternity of NIH scientists and a few hand-selected ethicists and consultants" to approve and disapprove all such experimentation. He said he believed this therapy offered medical benefit but that it could be used as a form of social and political discrimination. The public needed to be involved in the debate, expertise needed to be broadened, and decisions should not be allowed to be made within a small, elite group of scientists at the NIH plus hand-picked consultants.

He said he hoped this would provide for a lively discussion about the ethical, eugenics, and medical benefits of the technology and an opening up of the debate to begin a process that was closed and locked the public out.

Dr. Musgrave said he took personal affront with the terminology Mr. Rifkin had used in referring to members of the Committee as "hand-selected," and noted his distaste for the use of such language. He then asked Mr. Rifkin if, on advice of counsel, he was charging NIH with not providing informed consent.

Mr. Rifkin said that his attorneys and NIH attorneys and the Justice Department would handle the intricacies of litigation but that his in-house counsel was present to address the informed consent issue. He said he stood by what he had said, that the people on the Committee were hand-picked and that it was a tradition on the RAC to maintain "a network of people who are congenial to the interests of the NIH and the interests of the scientific fraternity and establishment." He cited as an example that until he had filed a lawsuit previously the RAC did not have an ecologist as a member, and that the ecologist who was finally appointed was no longer a member. He said that "you don't have people in this room who have a significant background in, for example, labor and discrimination at the workplace and a background in disabilities."

Dr. Musgrave asked Mr. Rifkin to simply answer the question as to whether, on advice of counsel, he was charging NIH with not providing informed consent. Mr. Rifkin replied that he did not mention in the lawsuit that he had mentioned the protocols. Mr. Kimbrell, attorney for the Foundation on Economic Trends, said the events leading up to the approval in the Subcommittee made the public sector very uncomfortable and that the approval was in violation of the "Administrative Procedure Act." He said the substance of the complaint filed in the U.S. District Court was that going back to the full RAC on a mail vote was a "significant change in protocol." He noted that copies of the complaint were available for review.

Mr. Carner said he was neither a "hand-picked consultant" nor a scientist, but that he viewed himself as a public member of the Committee and that he had offered the

motion which moved the issue forward because he felt it was long overdue. He said his view was that the Committee was not a "hand-picked, small elite group."

Dr. Walters noted that the President's Commission on Bioethics had considered gene therapy, that Congressman Gore had held hearings on this subject, that the National Academy of Sciences had held meetings on this subject, and a report of the Congressional Office of Technology and Assessment had also looked into gene therapy. He said he knew of no branch of biomedical science and technology to receive such "anticipatory scrutiny," and that a consensus exists that somatic gene therapy is an "ethically acceptable approach" to the treatment of certain diseases, provided certain safeguards are included in the proposals. He said he was "disappointed to hear about the lawsuit," and that the procedures that had been followed were entirely appropriate and reflective of an international ethical consensus on the acceptability of such work.

Ms. Mary Jane Owen, Director, Disability Focus, a Washington-based policy analysis organization, said she wished to report a "terror" which she thought existed among the public and disability advocates which had not been reflected. She said there was a large proportion of the public which was ill-informed of the RAC activities but terrified at their implications and that these deliberations were the "beginning of a slippery slope that you may not be able to control."

Mr. Martin Gerry, an attorney at law, said he was not affiliated with Mr. Rifkin or the lawsuit, but that he had certain concerns. A member of the Disability Advisory Council, Mr. Gerry reviewed his employment history and involvement with drafting regulations on human experimentation following the Tuskegee experiments. He said his concern was the potential for abuse in such experimentation. He said his concern was based on his experience in the field and uncertainties in the documentation of the proposal.

Mr. Gerry noted in the Tuskegee experiment a number of elderly black patients were intentionally infected with syphilis in an effort to study its epidemiology. He also cited the case of children at Willowbrook, a mental retardation facility in Staten Island, New York, who were intentionally injected with hepatitis-B virus in an effort to study the epidemiology of the disease. The rationale for this experiment was that the conditions in the facility were such that the children would have contracted the disease anyway and it could be studied in a more appropriate manner. He also mentioned an ongoing case pending against the University of Oklahoma Health Sciences Center in which an experiment took place from 1980-1985 on infants born with spina bifida. Thirty deaths were alleged to have occurred while testing a formula developed to determine which infants should be given active medical treatment and which should not.

Mr. Gerry said the proposal before the RAC did not represent any of the episodes he cited but, "the potential for abuse in terms of medical experimentation, in my experience, is clearly substantial." He said the members of the RAC should be concerned as to the circumstances under which such experimentation will take place.

Mr. Gerry stated that the rights of terminally ill patients are no less than the rights of others and their condition should not make it easier for the Committee to include them in this experiment. Major questions concerned him, namely: the method for selecting the subjects; whether the subjects will be compensated, and if so, under what circumstances; and the entire question of whether true informed consent can be obtained in this patient population.

Mr. Gerry said he had done an extensive amount of research on the subject of informed consent in the context of withdrawal of treatment from infants which showed that in periods of psychological trauma, it is difficult to obtain informed consent. He said this is also true of individuals who are aware they have a short period to live, and he had not found any information in the materials he had reviewed that outlined the procedures that would be followed to ensure the consent was truly informed.

Mr. Gerry said the structure of the experiment as described raised questions as to whether certain groups of people would be selected as subjects, out of proportion to the natural population. He said he found no comfort in picking terminally ill patients as subjects because despite understanding the risks of unintended life-threatening consequences, he had concern over infliction of pain that was no more warranted in this group than any other. He added the long-range implications of the experimentation should be addressed also.

Mr. Gerry said there were enough questions about the experiment in addition to the delays in Subcommittee approval, that the experiment should not go forward until greater discussion had occurred with opportunity for meaningful public input.

Dr. Murray corrected Mr. Gerry, noting that in the Tuskegee experiment the subjects had acquired syphilis naturally, rather than being deliberately infected. The ethical concerns were based on the fact they were not treated for the disease.
Mr. Gerry said it was more correct to say they were "not prevented from acquiring the disease or treated."

Dr. Murray said Mr. Gerry's point was irrelevant and he hoped the members of the Committee would concern themselves with the issue before them, namely the gene transfer experiment.

Dr. Walters said he had discussed the consent form to be used in the experiment with Dr. Alison Wichman, Chief of the Bioethics Program at the NIH Clinical Center, and that it may be useful to RAC members and the general public if that document were made available. He said it shows a conscientious effort to give full information to the study participants. He also said he wanted to correct one point which was that the Subcommittee recommended deferral of the proposal initially, but at the December meeting, all members recommended its approval.

Dr. McGarrity asked for other comments, and hearing none reminded the Committee that this was a "status report," which was not published in the Federal Register but

was included to update the Committee. He reiterated that the appropriate vote on the issue was taken by the RAC at its October 3, 1988 meeting. The mail ballot was not signed by him as Chairman but was signed by Dr. Moskowitz of NIH, underlining the fact that this was not a formal vote on the issue having been decided by vote of the Committee on October 3, 1988. Dr. McGarrity thanked all of the participants in the discussion and asked that the Committee move on to consider the next agenda item.

IV. PROPOSAL TO RECOMMEND AMENDING THE RECOMBINANT DNA ADVISORY COMMITTEE CHARTER:

Dr. McGarrity opened the discussion by restating that the consideration of the human gene transfer protocol submitted by Drs. Anderson, Rosenberg, and Blaese had been running on parallel tracks.i.e., it was discussed by the Subcommittee while a procedure also was in place for it to be brought before the full RAC. He noted this situation was unusual but that it followed existing procedures. However, now it had become clear that final action by the Subcommittee, before coming to the full Committee, would have been more prudent.

To avoid such occurrences in the future, Dr. McGarrity said a modified procedure should be examined. He called the Committee's attention to the first page of Tab 1347, at the bottom of the first paragraph where it is stated that the goal of this Committee is to recommend guidelines for the conduct of recombinant DNA experiments. This Committee is a technical committee established to look at a specific problem.

Dr. McGarrity noted that the RAC charter lists Subcommittees of the RAC and the ones that would be affected by amendment of the charter would be the Human Gene Therapy Subcommittee, the Plants and Associated Organisms Subcommittee, the Subcommittee for Revision of the Guidelines, and the Risk Assessment Subcommittee. He then asked Dr. Wyngaarden for his comments.

Dr. Wyngaarden said a codification of the review process was necessary to regularize procedures in the future and that he and the Chairman of the RAC and the Acting Executive Secretary of the RAC thought that the amendment before the Committee would result in a more logical, step-wise decision-making process. He noted this could not be done through a revision of the NIH Guidelines because they do not address the review process in detail, but that a change in the RAC charter would be a more appropriate means to accomplish this task. Because the charter is a document signed by the Secretary, Department of Health and Human Services, the proper bureaucratic action would be for the NIH Director to recommend to the Secretary that such a change be incorporated in the charter. He asked the Committee for help in framing such a recommendation.

Dr. Wyngaarden said the suggested wording of the change in the charter, as published in the **Federal Register** notice, is as follows:

"All proposals referred to a subcommittee for formal review must be approved by a majority of subcommittee members before being submitted to the parent committee. If a proposal is rejected by a subcommittee, the investigator may appeal this decision by application to the Director, NIH."

Dr. Wyngaarden asked for comment and discussion of this proposal.

Dr. McKinney suggested that since matters presented to subcommittees are in fact referred from the parent committee, the appropriate action would be to have the report from the subcommittee returned to the parent committee for consideration and comment. Then, if necessary, it could be appealed to the Director, NIH, thereby keeping the parent committee informed of the subcommittee's deliberations and actions.

In retrospect, Mr. Mannix said what should have occurred with the human gene transfer protocol is that the RAC should have entertained the Subcommittee's motion for deferral to allow for time needed to discuss the proposal. He said there was a risk in putting more emphasis on the decisions of subcommittees versus the full Committee in that it places more hurdles before investigators and may create a bias toward slowing research. He noted that proposals already must go through an IBC, an IRB, two levels of committees and then meet requirements of other agencies, and expanding this process was worrisome.

Dr. McGarrity asked if such fears could be set aside by setting up a timetable whereby subcommittees could be scheduled so as to meet and vote on matters and still be in cycle for the next full RAC meeting. Mr. Mannix said it would. However, he realized the problems inherent in doing so in that it could present difficulties for persons who may be planning to attend the full committee meeting to discuss a proposal scheduled for RAC review but which, for some reason, is not approved by the subcommittee. Dr. McGarrity responded that staff had discussed this and all attempts would be made to get proposals before the full Committee in a timely fashion.

Dr. Musgrave said he was opposed to this change in the charter because of concern that there does not seem to be any lobbying on behalf of the public who want these experiments to proceed. He said there appears to be an asymmetry between persons pushing for the saving of lives and progress of man's understanding and those whose views are in the opposite direction. He said he did not think it was in the best interest of science to create a series of hoops for investigators to jump through and that if the members of the RAC could not evaluate what is said and produced by a subcommittee he did not know who could.

Dr. Neiman pointed to the fact the Human Gene Therapy Subcommittee did not vote "no" on the proposal, but unanimously voted to defer making any recommendation until they had received the basic technical information on which to base a recommendation. The request to allow the Subcommittee to do its work was made

by every member of the Subcommittee present at the October 3, 1988 RAC meeting. He said Dr. Wyngaarden's proposal would, at a minimum, set up a process to allow the Subcommittee to act, thereby giving the full Committee a basis for discussion incorporating review of technical information that could not be addressed and debated in detail at the full Committee level.

Dr. Neiman said he was not concerned with whether the Subcommittee needed to approve a proposal before it went before the RAC, but simply that it be allowed to complete its deliberations of the proposal before full Committee discussion and action. He said he would be satisfied with a proposal that said, "the parent Committee will not act on a proposal until the Subcommittee has had a chance to do what it's been asked to do."

Dr. Murray said he agreed with Dr. Neiman, particularly because the enactment of the current proposal would prevent the RAC from being able to consider an issue that may receive approval from the full Committee but, for reasons of differences of opinion, may not be approved by the Subcommittee. He said more flexibility was needed to allow the RAC to hear what the Subcommittee is considering and to act if there is an important need to do so. Otherwise, Dr. Murray concluded, this could produce a situation similar to those in some legislative bodies where a bill or legislation is held up for extended periods of time in subcommittees and the full body is prevented from deliberating the issue because a minority does not want it discussed.

Dr. Murray said it wasn't important that the RAC might approve a proposal over objections by its technical experts, but that it was important to hear the rationale for rejecting a proposal and to be able to question the experts.

Dr. McKinney said he believed the role of the Subcommittee was to provide recommendations back to the parent Committee, which is charged with the decision-making. He suggested adjusting the language of the amendment to reflect the idea that the Subcommittee would bring their recommendations back to the parent Committee and this would provide the latitude to allow for an orderly process.

Dr. Pagano said he was concerned about negative Subcommittee recommendations not going to the parent Committee. However, he felt the parent Committee had the prerogative to either ask the Subcommittee to reconsider the question, or question the Subcommittee's decision, or appoint a different subcommittee. He said this was the role of the parent Committee and he did not object to receiving negative subcommittee recommendations.

Dr. Musgrave asked for clarification as to how subcommittee appointments were made and whether the full Committee appointed members of subcommittees.
Dr. McGarrity replied that the Committee does not appoint members.

Dr. Musgrave said this proposal would allow the subcommittee veto power over what could be brought to the full Committee and that this was a serious policy mistake. Further, he added, this gives additional power and responsibility to members of the

subcommittee, which is inappropriate. He said the idea that the subcommittee should expeditiously reach a decision and inform the RAC is an outstanding one, but to give them veto power is inappropriate. Further, the NIH Director can always institute a policy that says, "if the subcommittee doesn't approve it, I don't approve it," and therefore no harm will be done by letting the RAC see the facts since they are advisory to the Director.

Dr. Wyngaarden said the intention of the amendment was to "make sure that the subcommittee had completed its deliberation and reached a recommendation before it is addressed to the parent committee." Further, if something were disapproved at the subcommittee level and the applicant desired reconsideration, it could be appealed. The intention of the appeal process would be to allow the Director to return meritorious appeals to the RAC for deliberation. Dr. Wyngaarden said the charter amendment may require some rewording but that this was the intention, and the goal was to ensure that the subcommittee be allowed to finish its review before consideration of the proposal by the RAC.

Dr. Musgrave asked if Dr. Wyngaarden would object to having the subcommittee simply complete their work and present it to the RAC for a full vote, whether approved or disapproved. Dr. Wyngaarden said he had no objection to that, but the intention was that there be some recourse for the investigator if the subcommittee disapproved a proposal so that it could not be "vetoed," as was suggested, or bottled up in subcommittee. Dr. Musgrave asked if a proposal was taking a long time in subcommittee whether or not it could be appealed to the Director for a decision. Once that decision were made, the proposal could be brought before the RAC, regardless of the subcommittee decision. Dr. Wyngaarden said the idea of having it come before the RAC regardless of the subcommittee vote was good.

Dr. Neiman noted for clarification that if the subcommittee felt it did not have the information to proceed with a decision on a proposal, that it stay in subcommittee and the RAC be appraised of this by means of a report that adequate information was not available to allow for discussion by the full Committee.

Dr. McGarrity said if a proposal is acted on by a subcommittee, it will be referred to the full Committee and that such referral can be in the form of a status report or in the form of looking for a motion to approve the decision of the subcommittee. He asked the Committee members to provide language in the form of an amendment to the charter.

Dr. Epstein offered the following wording:

> "All proposals referred to a subcommittee for formal review must be approved or disapproved by the subcommittee members before being submitted to the parent committee.
>
> "If a proposal is rejected by the committee, the investigator may appeal this decision to the RAC."

Dr. McKinney asked Dr. Epstein how he would handle the deferral issue. Dr. Epstein said a deferral was a non-vote and the issue would be continued in subcommittee. It would not come before the full Committee unless it had been approved or disapproved by the subcommittee. Mr. Mannix said he was worried that this could result in indefinite deferral of some experiments.

Dr. Neiman said some leeway had to be given to take into account the competence of the members of the subcommittee. Perhaps the RAC Chairman could ask for a status report to the full committee when an application has been in subcommittee for an extended period of time, he suggested.

Dr. Walters said a reciprocal trust must exist between the parent committee and the subcommittees and that if a particular subcommittee became entirely unreasonable he would anticipate the RAC might dismiss all the members and replace it with a new group of people.

Dr. Murray suggested the following wording be included in the amendment:

> "The RAC reserves the right to review the deliberations of any subcommittee at any of its meetings."

Dr. Murray said this would allow a review by the RAC to see what is delaying a decision by the subcommittee without violating any procedures.

> Mr. Mannix moved the following:
>
> "A vote by a subcommittee to approve or disapprove an experiment go directly to the RAC for consideration. A vote to defer, if it were repeated, could be appealed by the investigators to the Director and he could decide on whether it was appropriate to move that to the RAC."
>
> Dr. Musgrave seconded the motion.

Mr. Carner said Dr. Murray's suggestion was excellent and asked that it be incorporated as a friendly amendment to the motion. Dr. Murray said he was not in favor of the motion because of the route of appeal to the Director. He said the NIH Director always has the authority to step in if he wishes to involve himself and this sets him up to act as an arbitrator between the investigator and the committee.

Dr. Musgrave suggested the current motion be amended to read:

> "A proposal approved or disapproved would come directly to the RAC; one that was deferred could be appealed to the RAC."

Dr. Epstein offered the following rewording:

"A motion which is deferred for two successive meetings of the Gene Therapy Subcommittee can then be appealed directly to the RAC."

Mr. Mannix and Dr. Musgrave both offered support for this wording as a friendly amendment.

Mr. Rifkin said questions had been raised over the role of the Human Gene Therapy Subcommittee and the scope of its mandate. He noted there had been some comment by Subcommittee members to the effect that they did not deem it appropriate to evaluate potential usefulness, but rather issues of safety only. He said there needed to be a discussion of which issues the Subcommittee will consider.

There being no further discussion, Dr. McGarrity asked Dr. Moskowitz for the exact language of the amended motion which was before the Committee.

Dr. Moskowitz re-stated the motion as follows:

"All proposals referred to a subcommittee for formal review must be approved or disapproved by a majority of subcommittee members before being submitted to the parent committee. If a proposal is deferred by a subcommittee for two successive meetings, the investigator may appeal this decision by application to the full committee."

Dr. McGarrity put the motion to a vote, and the motion passed unanimously.

At this point, Dr. McGarrity called for the morning recess and asked the Committee to reconvene at 10:35 a.m. After the recess, Dr. McGarrity called on Ms. Witherby to present the next agenda item.

V. REVIEW OF PUBLIC INFORMATION BROCHURE:

Ms. Witherby recounted the history of the document entitled, "Gene Therapy for Human Patients: Information for the General Public." She reported that she had presented the first draft at the August 1986 meeting of the Human Gene Therapy Subcommittee and the current draft is the seventh, therefore, the suggestions of many members of the Subcommittee, both past and present, have been incorporated into the brochure. She noted this version is the one for which approval is being sought.

She said, however, the current revision (Tab 1351) still needed some slight corrections and she would cover each of them.

The first correction is that the title of Part 1 in the Table of Contents should be changed from "DNA and Cells: Diseases and Their Treatment," to read "Diseases and Their Treatment." This would make the title consistent with text on page ii in the descriptive paragraph under Part 1. Also, the Subcommittee membership list is missing from the Table of Contents.

Ms. Witherby said the next change occurred on page 1 of the document where once again the title should now read "Diseases and their Treatment." On page 2, the first paragraph, fifth line, there has been a suggestion to replace the phrase "genetic engineering" with "gene insertion." Ms. Witherby asked Dr. McGarrity if these points should be discussed at this time, or after all corrections had been noted. He replied that he thought it wiser to cover them at this time.

Ms. Witherby asked for comments on the phrase "gene insertion" versus "genetic engineering." Dr. McGarrity said he misunderstood her and that he assumed she would go through the entire list and if there were no comments it could be assumed that participants agreed with the changes.

Ms. Witherby said on page 2, third paragraph, eleventh line, the sentence should read "After the cells to be treated have been temporarily removed from a patient's body, the virus or vector...." thus removing the phrase "so that" between "body" and "the virus."

She noted on page 3, the first paragraph, first sentence, the word "permanent" should be inserted, to change the sentence to read, "The best outcome of human gene therapy would be a single treatment that would correct enough cells to provide a permanent cure for the patient's disease."

Next, on page 3, under Part 2, second paragraph, sixth line, and the word "standards" should be deleted. The sentence will read: "First, hospitals and universities involved in experiments with human subjects are required to have Institutional Review Boards (IRB) to ensure that the research complies with the Department of Health and Human Services (DHHS) regulations for protection of human subjects."

Ms. Witherby said those were the significant changes in the paper itself but that discussion was required on the deletion of some of the "suggested reading." It had been suggested that the citation of articles in Science Digest, The American Journal of Medicine, and The Boston Globe be deleted from the list. Further, the membership list to be published in the document will include names of all Human Gene Therapy Subcommittee members, both past and present, who worked on the document.

Dr. Walters thanked Ms. Witherby for her efforts in preparing and compiling this document. He said it was important that the RAC try to communicate to the lay public what gene therapy and genetic approaches to the cure of disease entail. He noted the major substantive change in this draft from the previous drafts was the inclusion of genetic approaches to the treatment of non-genetic diseases. He noted the first human gene transfer protocol, in fact, dealt with the application of genetic techniques to monitor an experimental cancer treatment. This experiment may be followed by future proposals to adopt a genetic approach to cancer treatment, which is why the text was changed.

Dr. Walters also noted the document covers the breadth of public discussions, both in this country and abroad, and is an indication of the extent to which the topic has been carefully considered by thoughtful people around the world.

Dr. Epstein congratulated Ms. Witherby on her efforts and said he had some inconsequential changes he would discuss with her, but had two or three substantive changes to suggest. His first suggestion was on page 2, second paragraph, which currently reads, "It seems likely that human gene therapy will also be used to combat certain diseases that are not genetic." He suggested replacing "that are not genetic" with the phrase "that may not be genetic," referring specifically to cancer. This would be consistent with page 1, where cancer is listed among things that have genetic etiologies.

Secondly, Dr. Epstein suggested that a sentence be added to the last paragraph on page 2, stating, "Therefore, the newly inserted gene could not be passed to the patient's future children." He said this is an issue which would be debated later in the morning, but that gene therapy as it was being discussed currently referred only to somatic cell alterations which are non-transmissible.

Dr. Epstein observed that the use of the phrase "permanent cure" as suggested by Ms. Witherby was excellent.

Dr. McIvor said he agreed with the changes as presented by Ms. Witherby and Dr. Epstein and that he thought great care had been taken to make this technology understandable to the general public. He noted further that, with the exception of the references, it was ready for publication.

Mr. McCreery said he had reviewed the document and thought it impressive and well done. However, he was uncomfortable with the term "genetic engineering" and he felt it was to everyone's advantage to select words that were not as technically involved. Dr. McGarrity asked if the proposed term "gene insertion" would satisfy that problem. Mr. McCreery said the sentence "Adding genes in this way is called "genetic engineering," could be totally eliminated.

Dr. Clewell said on page 3, Part 2, second paragraph, seventh line, the term "recombinant DNA" is used for the first time in the document and he suggested the term be replaced with "gene insertion" to remain consistent throughout the document.

Dr. McKinney said on page 4, second paragraph, first line, the language suggests the NIH has authority over all federally funded research and suggested it may be helpful to define NIH jurisdiction. Dr. Tolin added that recognition should be made that other Federal research agencies have adopted the NIH Guidelines. Mr. Mannix also raised the issue that there is a distinction also between Federal agencies adopting the NIH Guidelines and private companies who comply with them voluntarily.
Dr. Walters suggested the sentence be rephrased to clarify this issue. Dr. Vidaver suggested stating that NIH has authority only over "certain" federally funded research.

Mr. Rifkin said he disagreed with changing the term "genetic engineering" to "gene insertion," since it is a phrase that has been used and accepted over time. He noted that engineering principles include predictability, quality control, ability to reduce phenomena to quantifiable standards of analysis, utility, and efficiency when dealing with inanimate objects, and those same set of assumptions are being applied to the genetics of plants, animals and humans. He said, "engineering is what this process is about."

He also noted two publications which were eliminated from the bibliography were Science for the People and GeneWatch. He said those two groups represent scientific opinion in this country and it appears that by dropping these references, a particular point of view is lost, thus prohibiting open and thorough discussion. He said these two publications have been involved in discussions of gene therapy from the beginning and there is no reason for the Committee to eliminate them simply because they don't share the same ideological perspective.

Mr. Rifkin said there was a "dangerous dichotomy being made here on the moral, ethical, and eugenics implications of somatic cell therapy versus germ line--a false moral and ethical dichotomy." He said germ line genetic engineering raises ethical and eugenics questions and that everyone agrees on this. But, he felt a consensus had been reached in the room that there are no moral, ethical, or eugenics questions raised by somatic gene therapy. However, Mr. Rifkin said, tremendous ethical problems are being raised by church groups, preventive health groups, minority groups, developmental groups, and disabilities rights groups, none of which have been involved in the process.

Mr. Rifkin presented a hypothetical situation where a scientist utilizing a somatic gene insertion could make someone less susceptible to a carcinogen in a particular environment. He said it would be easy to imagine a corporation giving preference in hiring to those having had such a treatment. He noted cases of such discrimination in the past when DuPont sought to minimize its liability by screening blacks for sickle cell anemia, and certain chemical companies in the 1970s who required female sterilization as a condition for employment in certain high risk chemical environments. He suggested that, "the major civil liberties questions of the coming decades are going to be the right of genetic privacy and the right of people to control their genetic make-up versus mandatory screening or mandatory genetic engineering of somatic cells in order to have people be congenial to the environments the corporations or institutions want to place them in."

Mr. Rifkin asked that the question of ethical implications of somatic therapy be discussed and that ethical and social questions should be raised in any brochure targeted for the lay public.

He concluded that the brochure does not begin to inform the public of all the costs and benefits of gene therapy. Furthermore, he claimed, this brochure was developed without reaching out for comment to minority, civil liberties, religious, or disability

rights groups to seek opinions on ethical impacts. Mr. Rifkin said he believed there were benefits to be derived from this technology but not having a vigorous debate on the ethical impacts of somatic gene engineering was a disservice to the public and an attempt to hide the real facts.

Ms. Witherby replied that Mr. Rifkin's concerns were premature and that the purpose of the brochure was to act as a current description of human gene therapy. There was no attempt to get into gray areas but, rather, to be absolutely informative and factual.

Mr. Mannix said he didn't believe anyone in the room believed somatic cell gene therapy was devoid of ethical implications, but the same kinds of ethical questions arising out of gene therapy also arise from surgical and chemical interventions in patients. In his view, the ethical considerations are dominated by informed consent, and by whether an intervention is beneficial to the patient. However, the issue of germ line gene therapy raises totally different ethical questions and this is why the Committee continues to make a distinction between the two measures.

Dr. Childress agreed with Mr. Mannix saying he believed there was an appreciation of the ethical significance of the questions surrounding somatic cell gene therapy, and that Mr. Rifkin was addressing was the question of abuse. In the future, the RAC may not be the particular body to address questions of abuse when the procedures have become routine and widely accepted therapeutically. There are other mechanisms in society such as the legal system to protect patients and workers. He re-emphasized that the same potential for abuse exists for other therapeutic procedures as well.

Dr. Murray said pages 6 and 7 of the brochure raise these issues but do not attempt to provide answers because there is no one answer in a heterogeneous society. Since 1970, he had been involved in debates regarding genetic screening and other technologies and their impact on minority groups. In Dr. Murray's experience, somatic cell gene therapy would be widely supported since, in spite of knowing the genetic code of sickle cell anemia, there is no effective therapy. He said there would be strong support for access to clearly stated, factual information on human gene therapy in the public literature. Moreover, Dr. Murray said he would vote to approve the brochure and support its dissemination if for no other reason than to stimulate further public inquiry, which is an important function of the brochure.

Dr. Walters, in reply to Mr. Rifkin's concern over the deletion of two references in the bibliography, said that all references to journals, news magazines, and newspapers had been eliminated from the reading list so that readers would not focus attention on any particular media. He also noted speculation as to the future events had been kept to a minimum so that he anticipated that the brochure would require periodic updating.

Dr. McIvor stated he proposed the phrase "gene insertion" in place of "genetic engineering" to reflect the accurate terminology for current technology. While Dr. Barbara Murray agreed with Dr. McIvor's intent, she said that "genetic engineering" is a commonly used lay term and, therefore, may be valuable.

Dr. Epstein noted that "engineering" is a term used to describe all aspects of recombinant DNA and not just gene insertion, which is the term of choice in the proper context.

Ms. Owen, Disability Focus, Inc., said that in the last 30 days she had spoken with members of her organization who voiced concern over the whole concept of genetic engineering. She said the social and discriminatory implications of gene insertion should be included in the brochure and the public should be encouraged to discuss these issues. She said everyone wants to alleviate discomfort and impairments, but the Committee needed to share the decision-making burdens with the public. The public information brochure would be an appropriate mechanism for both educating and involving the public in these discussions.

Dr. Walters noted that Dr. Childress had neglected to mention that he was a member of the Congressional Biomedical Ethics Advisory Committee (BEAC), a body that is looking at human applications of genetic engineering. Two of the topics before that Committee will be human gene therapy and eugenics. Mr. Alexander Capron, a member of the Human Gene Therapy Subcommittee, is Chairperson of the BEAC and Dr. Walters advised participants that it may be a very appropriate forum for the issues being discussed.

In the spirit of trying to protect individual rights of participants in human gene therapy, Dr. Murray suggested that the word "discrimination" be placed in the section on potential harm from the treatment to make it clear that people are aware of that issue.

Dr. Musgrave said the word "discrimination" was a "red flag" and an unlikely possibility. Its inclusion in this document would be used to manufacture fear. He concluded that nothing Mr. Rifkin attributed to the potential risk of discrimination associated with gene therapy could not be applied to automobiles and that if such an addition were made he would vote against it.

Disagreeing with Dr. Musgrave, Dr. Murray reminded RAC members that when the "Points to Consider" were originally formulated, there was a debate about why human gene therapy needed special consideration since it conforms to all other medical therapy. The conclusion was that gene therapy was special in that it signaled an advance in medicine that required special attention, and for this reason "discrimination" ought to be included in this list.

Secondly, Dr. Murray said, if the term "genetic engineering" was used in its broadest context, the manipulation of genes, and not merely gene therapy, there are ways it could be used to identify persons who could be discriminated against and, in fact,

there is evidence this occurs. He said he did not want to communicate to the public the perception that the Committee had failed to recognize this possibility. Dr. Murray felt that it was important to convey the sense of the Committee that genetic engineering should not be applied for the purpose of discrimination.

Dr. Childress said he shared the concern over the potential for discrimination. However, he said this discussion should be placed in another area of the document as the section being discussed focuses on the responsibilities of RAC and its subcommittees.

Dr. Musgrave said it was important that such fears be balanced with benefits in the document so as not to place undue emphasis on them.

Mr. Evan Kemp, a Commissioner on the Equal Employment Opportunity Commission (EEOC), said such issues were already present in the workplace along with others such as fertility and reproduction, and that they needed to be addressed.

Dr. McKinney said the term "discrimination" should be kept in its broadest interpretation and that to narrow its use would prevent the issue from being dealt with effectively.

Ms. Owen reiterated Mr. Gerry's concern that the selection of subjects for the human gene transfer experiment is an example of discrimination in that it had been determined that placing these individuals at risk was acceptable, due to their short life expectancy. In many cases, she stated, medical professionals, when faced with a patient who has failed available therapy, turn away from them thereby exhibiting a form of discrimination.

Dr. Riley suggested the Preface would be a better place to introduce this issue and that the third paragraph could be modified to state:

> "Many benefits are foreseen. However, because of the novelty of the field, concerns about eugenic misuse of the techniques, and possible affects on future generations from some types of human gene therapy, important ethical questions will also be raised."

Dr. Riley said the statement belonged in the Preface rather than the body of the document, which was designed to be scientifically factual. Mr. Mannix seconded the suggestion.

Mr. Kemp said the legal definition of "discrimination" was included in the Civil Rights Act of 1964, the Rehabilitation Act of 1973, and the Age Discrimination Act. He said the discussion of discrimination showed him the membership of the RAC needed to be broadened to include persons knowledgeable in the field of discrimination.

Dr. Musgrave responded that discrimination was a charged topic. He said discrimination is value-based and that if scientific terms were to be used in the document he suggested "testing and evaluating" rather than "discrimination."

Mr. Mannix said "discrimination" was an ambiguous term with good and bad connotations and that it ought to be raised in a context that acknowledges ambiguity and a wide range of opinions. Therefore, he felt it would be appropriate to have it addressed in the Preface, as Dr. Riley suggested.

Dr. Epstein asked the Chair for clarification on the Committee's role. Dr. McGarrity said it would be appropriate for the Committee to move, second, and vote approval of the document, along with modifications proposed by Ms. Witherby and others, and any contention over specific issues such as the issue of discrimination could be handled by a separate vote of the Committee.

Dr. Epstein moved the Committee approve the document with modifications proposed by Ms. Witherby in her introduction, with his own recommendations and with Dr. McIvor's recommendations, i.e., the insertion of the phrase "concerns about discrimination and eugenic misuse" in the Preface, changing "genetic engineering" to "gene insertion," et cetera. Dr. Riley seconded the motion.

Dr. Musgrave asked if the term "testing and evaluation" could be put in parenthesis following the word "discrimination" in the Preface. Dr. Epstein said he felt it fair not to modify it since the term "discrimination" and "eugenic misuse" were the concerns that had been expressed.

Mr. Gerry suggested the term be modified to state "unlawful discrimination." He said he supported Mr. Kemp's statement that discrimination based on health issues exists in the workplace and that in a subject area as charged as human gene therapy there is a substantial likelihood that employers will misunderstand, misinterpret, or abuse the situation. He said that there are 6.5 million people receiving federal disability benefits under SSI or SSDI. Half of these people could be gainfully employed but for discrimination in the workplace or a combination of disincentives under federal programs that discourage them from working. Mr. Gerry said employer attitudes and behavior were very germane to the issues under consideration.

Dr. Childress suggested a modification to say "concerns about the discriminatory and eugenic misuse of the techniques," which he said improve the sentence read better and capture the sense of the Committee.

Addressing the use of the term "genetic engineering," Mr. Brewer said that in the interest of using precise terminology, the term "gene insertion" might be accompanied by the statement that it is popularly referred to as "genetic engineering."

Dr. Musgrave asked Dr. Epstein if he would approve of changing the term to "unlawful discrimination." Dr. Epstein replied he would not agree to that because he would view it as an oxymoron. He said he thought all discrimination was essentially

unlawful or unethical in that the term is being raised in a negative context to begin with. Mr. Mannix asked Dr. Epstein if he would accept Dr. Childress' language. Dr. Epstein said he would accept the use of the phrase "discriminatory and eugenics misuse of the techniques," if it were syntactically better. He added his support to the suggestion made earlier to delete the whole sentence that included the term "genetic engineering" and asked Dr. Riley if, as the seconder of his motion, she would agree with that, which she did.

Dr. Schaechter said the purpose of the document was to communicate with, and not to the public and the term "genetic engineering" was understandable and should be adopted. Mr. Brewer said "genetic engineering" is a term, like "discrimination," that has both positive and negative connotations. Mr. McCreery asked that the whole sentence be removed.

Dr. Erickson suggested the sentence be moved to the Preface, and to have it stated:

> "The possible new treatment is called human gene therapy and is one of a series of emerging genetic techniques, commonly called 'genetic engineering' based on new knowledge about how genes work."

Dr. Epstein said he would accept this amendment. He agreed that moving it into the preface and taking it out of the factual text of the document would be preferable.

Mr. Mannix called the question. Dr. Murray seconded the motion. Dr. McGarrity put the motion to call the question to a vote. The vote was unanimous, with no abstentions. Dr. McGarrity then called for a vote on Dr. Epstein's motion to approve the public information brochure, as amended. The vote was 23 in favor, none opposed and no abstentions.

On behalf of the Committee, Dr. McGarrity complimented Dr. Walters and his Subcommittee for their efforts, particularly Ms. Witherby for her dedication and devotion in developing the public information brochure. Dr. McGarrity then asked that the Committee turn its attention to the next agenda item at Tab 1352.

VI. PROPOSAL TO AMEND SECTION IV-C OF THE NIH GUIDELINES:

Dr. McGarrity said he was confused as to the exact definition of the term "eugenics" and asked Mr. Rifkin, the proposer of the amendment, to give his definition of the term.

Mr. Rifkin said eugenics had a long history, going back to Plato's Republic. Francis Galton's definition, modified in popular terms, was genetic manipulation to change, or generally, to improve a species, a human being, an individual, or a population, or the human species, somatic or germ line; within the context of the social implications that can arise from that manipulation.

Dr. McGarrity thought it might be useful for all participants to start at the same baseline so he offered the following definitions:

> Webster's Dictionary defines "eugenics" as: "a science that deals with the improvement, as by control of human mating, of hereditary qualities of a race or breed;"
>
> Dorland's Illustrated Medical Dictionary defines "eugenics" as: "the study and control of procreation as a means of improving the hereditary characteristics of a race, also called orthogenics. Positive eugenics concerns the promotion of optimal mating of individuals possessing superior or desirable traits."

Dr. McGarrity referred the Committee to previous minutes of the RAC and the Human Gene Therapy Subcommittee as well as the "Points to Consider," which note a distinction between somatic cell gene therapy and germ line gene therapy. He reiterated the point that the Committee will not entertain motions that involve reproductive cell gene therapy. He said human gene therapy, as it pertains to the RAC, involves curing of a specific disease, not breeding. He repeated this in layman's terms for the audience saying that human gene insertion will affect only the patient, not future generations. He called on Dr. Childress for his comments.

Dr. Childress said he appreciated the concerns raised by the petition but did not believe it should be supported or accepted because of existing mechanisms at NIH and elsewhere, that are available to meet all of the concerns expressed.

He disagreed with the petition's criticism that the RAC and the Human Gene Therapy Subcommittee were insensitive to concerns of eugenics and said these comments were misdirected, unsubstantiated, and unfair. He said one charge was that RAC members and members of the Subcommittee were "interested primarily in advancing medical research and commercial applications resulting from that research." He noted that such charges were unfair if they meant that members, whether scientists or non-scientists, would choose to advance medical research and commercial applications over the legitimate interests of those affected by the research. Furthermore, public participation in meetings was sufficient to make sure all interests were heard, whether or not they were directly elicited by the Committee. He said the charges of inadequacy of the RAC and Human Gene Therapy Subcommittee to address concerns related to human somatic cell gene therapy were unsubstantiated in the petition.

Secondly, he said the petition's concerns go beyond human gene therapy and well beyond NIH-funded research and focus more on mapping the human genome and genetic screening, which are better addressed elsewhere.

Finally, Dr. Childress said there are other forums and institutional mechanisms for addressing the broader concerns such as the Biomedical Ethics Advisory Committee and the Congressional Biomedical Ethics Board. He said the function of these two

bodies is, "to study and to report to the Congress on a continuing basis on the ethical issues arising from the delivery of health care and biomedical and behavioral research, including the protection of human subjects of such research and developments in genetic engineering, including activities in recombinant DNA technology which have applications for human genetic engineering." He noted that the Biomedical Ethics Advisory Board is now functioning. One of its mandated reports will be on human genetic engineering including human gene therapy and the Human Genome Project, genetic testing and screening, and eugenics and public policy. He said this report would cover virtually all of the areas of concern raised by the Foundation on Economic Trends and would provide ample opportunity for public input as suggested by this proposal.

Dr. Schaechter asked for clarification as to whether the RAC had authority in fact to set up a parallel and equal structure to look at these issues. Dr. McGarrity said the RAC can make amendments to the NIH Guidelines but does not have the authority to set up another committee. This rests with the Director of NIH or the Secretary of DHHS. However, Dr. McGarrity said because of the visibility of the issue and the fact that the proposal had come before the Subcommittee, it may be in the best interest of the Committee and the general public to discuss the motion.

Dr. Mulligan asked Dr. Wyngaarden for his opinion as to the appropriateness of the RAC voting on the establishment of a committee which it cannot constitutionally establish. Dr. Wyngaarden said he didn't know whether such a vote was permitted or not, but that an expression from the Committee might be useful despite the RAC not having the authority to establish a new committee.

Mr. Mannix said he agreed with Dr. Childress' statement. He went on to note that the RAC is advisory to the Director of NIH and that the use of parliamentary procedure is meant to discipline the process, not to suppress minority points of view. If a significant disagreement exists in the Committee, both the Chairman and the Executive Secretary have a duty to report to the Director not simply what the majority voted, but also minority points of view that were expressed.

Dr. McGarrity reiterated that the options are always open to submit a minority report under Robert's Rules of Order.

Dr. Erickson said he wanted to add two points. First, the Committee already has members versed in each of the six areas of expertise mentioned, including occupational safety and health and perinatal testing. He said perhaps it was the proportion and viewpoint on these areas that was being questioned by the proposal. Second, he pointed out there are many other committees that review these areas such as the NIH Human Use Committees, which include ethicists and other individuals mentioned in the proposal. Dr. Erickson added that setting up another such committee would just add another layer of bureaucracy.

Dr. Acosta said that in light of the definitions and concepts outlined by Dr. McGarrity as to the limitations of somatic cell therapy, the premise that attempts would be made to "improve the human species," as defined by Mr. Rifkin, would be contradictory to the present Human Gene Therapy Subcommittee policy. Further, she observed that Mr. Rifkin has proposed a committee similar to the RAC in composition but with a mandate to advise the NIH Director on the ethical, philosophical, social, economic and eugenics implications without addressing the technical, biomedical, and biological aspects of the eugenics that are defined as "improving a species."

Mr. Carner moved the following:

> "The RAC expresses appreciation to the Foundation on Economic Trends for directing the attention of the RAC Committee to the question of establishing a Human Eugenics Advisory Committee and that the RAC Committee respectfully declines to approve the proposal."

Dr. Musgrave seconded the motion.

Dr. McGarrity made the observation that there were two options open to the Committee: (1) to vote on such a motion as was made by Mr. Carner; and (2) to simply have no motion at all.

Dr. Musgrave withdrew his second and asked for clarification of the two courses of action. Dr. McGarrity said the alternate course of action simply would be to make no motion, and therefore all persons could have their viewpoints heard but there would be no motion on the table. Dr. Musgrave repeated his withdrawal of his second to the motion.

Dr. Erickson then seconded Mr. Carner's motion.

Dr. Epstein said the definitions presented varied in that the dictionary definitions related eugenics entirely to modification of future generations, whereas Mr. Rifkin's definition included somatic cell modification of individuals, which is not considered eugenics by either of the dictionary definitions or by geneticists. He said it was an unfortunate choice of words to be raised in connection with human gene therapy because it conjures up concerns that are not relevant to somatic cell gene therapy.

Dr. Musgrave moved to call the question. Dr. Epstein seconded the motion. Dr. Childress asked if there should be public comment before calling the question. Dr. McGarrity said that the Committee could choose to vote against the motion if it desired to continue discussion.

Dr. Musgrave said he would like to hear from the presenter and therefore he withdrew his motion.

There being no further comments from the Committee, Dr. McGarrity called on Deborah Kaplan, Director of Public Affairs, World Institute on Disability, Berkeley, California.

Ms. Kaplan said she went to great trouble to come to the meeting from California and that the issues that were raised in the petition were relevant to the deliberations of the RAC. She said the more public input the Committee could have, the better off it would be. She said she believed the NIH did not convene the RAC merely to have it vote on issues, but that the advice it offered to the NIH was important and had great weight in setting policy, both nationally and internationally.

She felt that the RAC should take the proposal more seriously and recommend to NIH that further discussion should take place on these issues. She said the input of public representatives who were not reimbursed for their time legitimized the views expressed since they have no particular interest other than their care and concern over matters being discussed. In Ms. Kaplan's view, the RAC should look for ways to get broader input although perhaps the RAC does not have the authority and power to recommend this to the NIH.

Ms. Kaplan said there was an assumption among clinicians and scientists that everyone agrees on what constitutes a benefit to an individual as a result of research; she suggested that this may not be correct. She related an anecdote in which a deaf couple went to a genetic counsellor wanting to know what the risks were of their having a hearing child. This was presented as an example of the difference of opinion as to benefits and quality of life that the disabled community could bring to discussions such as this; not that such opinions should predominate, but that they should be expressed.

She said the issue of benefit as it relates to care was not clear-cut. For example, treatment of disabling conditions entails certain trade-offs, such as removal from the sub-cultures to which these people have become accustomed. Not everyone would choose to accept the cure. Further, she expressed concern that social pressure, family pressure, pressure from the medical community and the insurance industry may supersede individual judgment about cures resulting from this technology. These are considerations worth discussing, she concluded.

Ms. Kaplan said representatives from the disabled community had much to contribute in that they were not scientists or precise people, but people who deal with social issues routinely. The social implications of such therapies need to be brought forward for discussion.

Mr. Rifkin raised a question related to either somatic or germ line genetic engineering, that is, the criteria for determining which genes are functional and dysfunctional and which are good or bad. This issue extends to which forms of somatic gene engineering are appropriate and which are not. This is why his proposal seeks to broaden not just the basis of public input but the basis of decision-making.

Mr. Rifkin said it was time to redefine eugenics because in Galton's time, the only way to engage scientifically in eugenics was through mating and seeing what was produced in the offspring. Today, through genetic engineering, it is possible not only to change not only the genetic instructions of the offspring, but to change the genetic instructions of an individual. For this reason, Mr. Rifkin said, it was necessary to broaden the concept of eugenics to include individuals, because if these experiments are successful, they could be applied to whole populations, or sub-populations, or cultures to gain an advantage for these groups.

Mr. Rifkin said there was a long history of the scientific establishment trying to separate out research and development of a technology from its social application. He said it was not sufficient to look at an individual genetic experiment and analyze the benefit to the individual separately from the potential social application because in the past this has created more social, cultural and ethical problems. He was sure that in the future somatic gene engineering proposals would come before the Committee that would have dramatic social impact on discrimination in the workplace and disability insurance. In his opinion, the RAC will not be prepared to deal with these issues.

Mr. Rifkin then asked if the RAC had set up committees in the past to deal with different issues. Dr. McGarrity explained that the Charter for the RAC comes from the Secretary of DHHS, who is empowered to establish advisory committees. Mr. Rifkin asked whether the Subcommittee on Deliberate Release had not been established by the RAC. Mr. McCreery said that group was constituted as an ad hoc working group, not a committee. Mr. Rifkin then asked if a similar group could be set up to look into the issue of broadening the base of opinion and expertise on the Committee. He announced that if this were not done, his group and groups like it would return to every meeting to continue to seek mechanisms to deal with the social, ethical and eugenics implications of somatic gene therapy. He stated:

> "This group cannot play God when it comes to deciding what genes should be engineered in and out of individual patients here in the United States. You're just not going to be able to maintain that control of power within a small group."

Dr. McGarrity said he did not want to cut off or limit debate but that he wanted to have enough time to complete the agenda, and asked for all comments to be brief, concise and non-repetitive.

Dr. McKinney said that since its inception the manner in which changes had occurred in the RAC had been from a factual perspective, not from an emotional perspective, and noted that the Human Gene Therapy Subcommittee had addressed many of these issues repeatedly in its long tenure. He said at this juncture he felt the addition of another committee was clearly premature.

Dr. Erickson observed that only one side was represented at this meeting, and that on the other side were the many disease-oriented volunteer groups who have voiced the

need for therapy. The Committee currently reflects all the views, and that perhaps the choice of choosing a therapy or not should be left to the patients. He said Mr. Rifkin's proposal implicated an existing denial of rights to patients with genetic diseases and noted that mechanisms such as Institutional Review Boards and Human Use Committees are in place to deal with these situations.

Dr. Walters made three points. First, he said that he shared concerns expressed about discrimination against disability groups and long term implications of genetic testing and screening. However, while Dr. Walters said that he found it frustrating at times that there was not a Subcommittee on Genetic Screening, there are other mechanisms to address these issues that will have to be relied upon to give timely notice to the RAC as problems arise. Secondly, he stated the best way to care for the disabled is to find new cures for disease. In his view there should not be a dichotomy between caring about disability groups and the practice of biomedical research and clinical medicine. Lastly, Dr. Walters observed that the major objections to the first gene transfer protocol did not come from ethicists and lawyers, but from laboratory scientists. The scientists raised valid objections that needed to be addressed by the Human Gene Therapy Subcommittee and the RAC, thereby accepting a major portion of the responsibility for protecting the patients.

Dr. Epstein affirmed Mr. Rifkin's statement that the U.S. has had a relatively poor record in the past with regard to eugenics. However, Dr. Epstein observed that human genetics, as is now practiced in the U.S., has turned in the opposite direction in the sense that the thrust of all current genetic counseling is to put the decision-making into the hands of those who are involved directly, that is, to provide them with information but not to stipulate the form of therapy they receive or the decisions they make.

Secondly, Dr. Epstein noted the first two items in the "Points to Consider," which are:

> "What disease do you intend to treat with the gene therapy?" and,
>
> "Why do you consider the disease to be an appropriate candidate for treatment with this method?"

Dr. Epstein said the Committee would not entertain gene transfer experiments such as those cited for the purpose of providing employers with people with resistance to carcinogens in the workplace because this is not a disease state and therefore does not meet the requirements of the "Points to Consider."

Dr. Musgrave said Mr. Rifkin and his colleagues had no knowledge of many of the other activities of the Committee members citing his work with the American Speech, Hearing and Language Foundation and work with blacks and other minority groups with which he was currently involved.

Dr. Musgrave called attention to the minutes of the December 9, 1988 meeting of the Human Gene Therapy Subcommittee (Tab 1346, page 50), page 13, the fifth paragraph, which states:

> "Dr. Anderson called attention to pages 201-204, a bibliography included as part of the proposed amendment to the Guidelines. When Mr. Rogers [Rapporteur's note: attorney representing the Foundation on Economic Trends] was unable to identify the origin of those references, Dr. Anderson replied that the bibliography was part of a preprint of a scientific paper that he had shared with Mr. Rifkin last month. Mr. Rogers apologized and agreed that this usage did constitute plagiarism."

Dr. Musgrave asked for an explanation of this. Mr. Andrew Kimbrell, attorney for the Foundation on Economic Trends, said that it was a bibliography that should have been merged with several other references. He added that he did not see the relevance of this point to the Foundation's proposal.

Dr. Musgrave responded that more than one university student had been expelled for plagiarism. This is a serious matter in science and material that comes to the RAC should meet the highest scientific standards.

Dr. McGarrity asked Dr. Anderson if he would like to give some background on the issue. Dr. Anderson said he found it amusing that a bibliography in a manuscript that he had given to Mr. Rifkin had been inserted directly, with no changes, into the very petition objecting to the protocol.

Mr. Rifkin said there was a miscommunication between his staff as to the origin of the bibliography. He said he agreed that plagiarism is a problem, but this was a miscommunication. Mr. Rifkin said he had published books himself and had never been accused of anything of this nature. He said the source should have been acknowledged and he asked the Committee and Dr. Anderson to accept his apology.

Dr. McGarrity then called on Janine Bertram, Coordinator of Public Relations for the Endependence Center of Northern Virginia, who read a statement by Hugh Gregory Gallagher.

Mr. Gallagher wrote that he was an author of articles and books on federal policy-making and minority rights, and he had worked on public policy matters both in and out of Government for 30 years. He outlined the case of physicians and scientists in Nazi Germany who believed they were operating according to scientific principles, applying the laws of genetics and findings of eugenics to social policy. He said the value system of doctors and scientists is culturally determined, their judgment determined by their culture and social status, and their understanding of reality a function of their experience.

Mr. Gallagher said the mapping of the human genome and developing skill in genetic engineering offer potential for immense benefits for mankind but also the possibility

of misuse, misapplication, unconscious social and racial parochialism, and the possibility of danger and destruction. He said genetic research policy should be made by elected policy makers, fully advised by scientists and informed of the views of interested parties and in public, and subject to all administrative policies and procedures and applicable law.

Mr. Gerry announced that he was not affiliated with Mr. Rifkin, and did not wish to become involved in what appeared to be personal disagreements between Mr. Rifkin and some members of the RAC. However, he was concerned that debate be allowed to continue. Mr. Gerry spent the past 8 years working closely with the Surgeon General on a series of difficult and controversial policy issues. Given this background, he thought that it was naive to think that human gene insertion will not be the subject of a great deal of public controversy. Further, he said he understood the proposal before the Committee requested the Director of NIH to establish a group composed of people other than RAC to look at the issue, and that it would be difficult for any Committee to criticize its own composition or membership. He said he did not feel the RAC was inadequate or lacked the appropriate people, but he felt such an entity needed to be created.

Secondly, Mr. Gerry said, this would broaden the base of advice for the NIH Director and the Secretary to support future decisions and to stem any legal challenge to decisions in the future. He said, "if the Secretary asked my advice, it would be to definitely create such a group because I don't think you can assume that without it you're going to be able to demonstrate that the specific objections that will be raised have been carefully considered by the Director."

Ms. Owen said that this is an opportunity to expand input and get additional information. She said that the medical profession has more fear of disabilities, vulnerabilities and frailty than the general population and there are some positive effects that transpire when people experience vulnerabilities and overcome them. Input of this sort would be valuable to the Committee, she concluded.

Ms. Owen presented a videotape presentation of a disabled author, Ann Finger, from Los Angeles, California. Ms. Finger said she had written and lectured about the history of the eugenics movement and dangers of what she called "neoeugenics" posed to disabled people. She analogized genetic engineering to the Manhattan Project saying that sickness and disability were the enemies and that the urgency of curing illness and disabilities was causing many of the negative impacts of the technology to be overlooked.

Ms. Finger also called attention to the eugenics movement in the early 20th Century and, in particular, to eugenics statutes in the United States and in Nazi Germany. She noted that despite the revulsion many people had for eugenics, it had widespread support from distinguished scientists, social reformers and people of good will who felt this was a method to cure hereditary diseases.

She used the case of asthma as an example of a disabling condition with a strong genetic component. She said that despite the negative impacts of asthmatics' sensitivity to toxins, there was a positive effect in that this sensitivity could be classified as an early warning system alerting others to the dangers of environmental pollution and could be viewed as actually a trait of superiority in this regard. Ms. Finger added that most disabled people were more handicapped by social attitudes and an exclusionary environment, rather than by the physical constraints of their disabilities.

Ms. Finger expressed concern that greater knowledge of human genetic structure could result in a genetic hierarchy and discrimination in the workplace. Therefore, she questioned the social and ecological value of genetic research.

Dr. Pagano said he thought everyone at the table was concerned for the problems of the disabled and was aware of the feelings expressed by Ms. Finger and others. Dr. Barbara Murray said she felt the comments that had been made were addressed as if the RAC were composed totally of M.D.s, who were actually in the minority, while the majority of the Committee members were Ph.D.s and non-scientists. She commented that any medical therapy had the potential for improving one person over another and reiterated the concern that this body was not the one to be considering these issues. Dr. Childress agreed with Dr. Murray and said the Biomedical Ethics Advisory Committee was indeed going to address the issue of eugenics, and that lay input would be sought in formulating their reports.

Mr. McCreery said he took offense at the accusation that all members of the Committee were narrow-minded and he sketched his participation over 40 years in national and international volunteer health care organizations, pointing out that there were many Committee members with equally diverse backgrounds and interests.

Dr. Musgrave said that he had no ill feelings toward Mr. Rifkin personally, but that he and his colleagues did not represent the views of the entire spectrum of disabled persons in the country. Returning to the issue of the bibliography, he noted that this was the means of assessing the reliability and integrity of an author and that since ethics was a concern being expressed by Mr. Rifkin, Dr. Musgrave wanted the plagiarism issue clarified.

Mr. Brewer said that despite the general feeling that doctors were narrow-minded in their focus, his experience on the Committee had shown that the physicians and scientists asked the most sensitive questions, not only in scientific and technical areas, but in ethical and social areas. He believed they should be judged as individuals and not characterized as a homogeneous population.

Dr. McGarrity reiterated his concern of completing the meeting on time and asked if there was any further discussion. Dr. Gellert moved the question on Mr. Carner's motion. Mr. McCreery seconded the motion. Mr. Carner repeated his motion that:

"The Committee expresses its appreciation to the Foundation on Economic Trends for directing the attention of the RAC to the question of establishing a Human Eugenics Advisory Committee, and that the Committee respectfully declines to approve the proposal."

Dr. McGarrity asked for a vote on the motion to end debate and call the question. The motion passed by a vote of 22 in favor, none opposed, and one abstention.

Dr. McGarrity then called for a vote on Mr. Carner's motion. The motion passed by a vote of 20 in favor, none opposed, and three abstentions.

Dr. McGarrity thanked all the participants for a lively discussion and noted that the final chapter in this discussion probably had not been written. He added he wished the record to reflect that Mr. Capron, a member of the Human Gene Therapy Subcommittee and Chairman of the Congressional Biomedical Ethics Advisory Committee stated he thought the topic was a more appropriate agenda item for the Biomedical Ethics Advisory Committee than for the RAC. He then called for the luncheon recess and asked members and guests to reconvene at 2:00 p.m., that afternoon.

VII. PROPOSED CHANGES IN APPENDICES P AND Q OF THE NIH GUIDELINES:

Dr. McGarrity reconvened the Committee at 2:04 p.m., and asked Dr. Vidaver to lead the discussion. He noted that tabs 1345 and 1348 were pertinent to the discussion.

Dr. Vidaver began by noting that currently Section III-B-4-b of the NIH Guidelines gives no assistance to IBCs in determining containment for experiments dealing with whole animals and plants. She said she wished to present general comments and a brief history of the issue since the membership of the RAC had turned over considerably since the first discussions of this topic.

Dr. Vidaver said inquiries to NIH and the U.S. Department of Agriculture (USDA) had indicated further guidance needed to be developed on containment conditions for whole animals and plants outside the traditional laboratory setting. The proposed Appendices P and Q would codify these practices and incorporate recombinant DNA technology into them. They also will be applicable to burgeoning technologies such as protoplast fusion experiments in plants and the use of microprojectile devices for animals, which would be the topic of a separate proposal before the RAC from the National Wildlife Federation.

Dr. Vidaver said the Appendices were discussed in the August 11, 1987 issue of the Federal Register; the September 21, 1987 minutes of the RAC; and the December 30, 1988 issue of the Federal Register.

Dr. Vidaver said as early as 1978, the USDA had realized that research would need to progress from the laboratory to greenhouses for plants and various types of facilities for animals before small-scale field tests of recombinant DNA experiments

could be performed. She said the Appendices were the result of several meetings of NIH and USDA working groups as well as recommendations from the RAC and USDA's Agricultural Research Service (ARS). She proposed that the Appendices be addressed separately, beginning with Appendix P for plants.

Dr. Vidaver said the rationale for development of Appendix P was threefold:

(1) It was recognized that neither plants, nor organisms associated with them, had essentially any recognizable health hazard for either higher animals or humans;

(2) The objective of the NIH Guidelines is to minimize the possibility of deleterious effects on organisms and ecosystems outside the experimental facility; and

(3) The need to protect the experiments from animals, plant pollen and microorganisms that would arise from outside the facility.

Dr. Vidaver noted a basic principle of the Appendices is that biological properties of the modified organism are the critical issue in designing containment, not the changes brought about by the technique, per se. Such characteristics are highly dependent on the original, unmodified organism and the original status or classification of the organism is the basis for decision making for physical or biological containment, according to Dr. Vidaver.

She noted that most of her proposed changes were to ensure consistency, such as the use of the term "arthropod" instead of "insect" to reflect the concern about small, mobile animal transmission, and for clarification or for omissions.

Dr. Vidaver said conditions for containment of plants would be designated at four levels, BL1-P through BL4-P, to correspond with the biosafety levels for microorganisms currently in the NIH Guidelines, and that in many cases these Appendices will replace physical containment requirements described in Appendix G.

Dr. Vidaver said she would deal with specific typographical errors and clarifications by paragraph as found in Tab 1345, and would be discussing them by paragraph number.

Dr. Vidaver said her first comment related to a suggestion by ARS that all run-off water be decontaminated. She said she did not agree with this, believing that it was not required in all circumstances with respect to both biology and expense. In her view, decontamination of all run-off water would be expensive and would not increase safety.

Paragraphs 117 and 139 refer to posting a biohazard sign. This suggestion was discussed previously by the RAC, concluding that experiments taking place at BL1-P and BL2-P did not require such signage. However, she suggested that signs be

retained at the BL3-P and BL4-P levels, but that due to the nature of plant research, they be required only if there is a risk to human health. She suggested changing the first sentence of paragraph 117 of Tab 1348 to read:

> "A sign incorporating the universal biohazard symbol and the name of the recombinant DNA-modified organism is posted on greenhouse access doors if there is a risk to human health."

In addition, the first sentence of paragraph 139 would be changed to read:

> "A warning sign incorporating the universal biohazard symbol is posted on all access doors if there is a risk to human health."

Dr. Vidaver noted that the potential for environmental hazard is recognized explicitly in paragraphs 113(a) and 136. She said she would favor a sign in both cases indicating a restricted experiment was in progress, but that it be recognized that plants and associated organisms do not normally pose a human health risk.

Dr. Vidaver turned to paragraph 133a, in which the ARS had recommended the use of a HEPA filter. She said she agreed with the recommendation but it was not clear where this sentence should be placed and asked for clarification from USDA personnel.

In paragraph 160, there was a recommendation that under BL4-P conditions reference to back-up electrical power should be eliminated, but Dr. Vidaver said she felt it should be considered. She said she did not feel it was necessary to make it obligatory, but that since there was only one facility currently operating at this high level of containment in the country and since new construction may rely on these guidelines, both nationally and internationally, it should be considered.

Dr. Vidaver then moved that the RAC accept the proposed changes in Appendix P, as amended.

Dr. McGarrity said he felt it proper to hear from other reviewers before entertaining a second to the motion and called on Dr. Sue Tolin, USDA liaison to the RAC.

Dr. Tolin said she had reviewed the changes and found the revisions recorded by ORDA in the section dealing with plants to be accurate. She said she had also gone back to the main NIH Guidelines to update them with changes recommended previously by the RAC and noted that paragraph 46 already had been modified to change it from BL3-P to BL2-P plus biological containment practices. She said the RAC had also added a sentence referring to toxins in Section III. In paragraphs 58 and 60, the addition of the phrase "in the immediate geographic area" was added in reference to plants which are noxious weeds or can interbreed with plants which are noxious weeds.

Dr. Tolin said she agreed with the ARS suggestion that paragraph 39 be modified but suggested a better place for this would be in Footnote 18 of the NIH Guidelines which refers to APHIS regulations regarding plant pests. She said final wording of the reference still needed to be worked out and that Dr. Payne of USDA had agreed to work with ORDA on specific language.

Dr. Tolin said her interpretation of paragraph 133a was that the HEPA filter was an alternative to the air supply filter, and since experiments at this level already require HEPA filtration on exhaust air, this was an option to be considered for the intake air supply. She said her recommendation was that the HEPA filter would not be necessary at the intake site.

Dr. Riley said she favored adoption of the modified provisions. She said there was agreement about the signage in paragraph 103a, but despite the implications of biohazard signs, some sort of signage was called for at levels BL2-P and above.

Dr. McKinney asked for clarification as to whether a motion to reconsider the Appendices was required in order to effect these modifications since the RAC had already approved and sent recommendations for changes in these areas to the Director, NIH, for approval.

Dr. McGarrity asked for a status report on Appendices P and Q. Ms. Levinson said the environmental assessment had not yet been completed. Dr. McGarrity noted that until the environmental assessment had been completed the proposed additions could not go to the Director, NIH.

Dr. McKinney said he understood that, however, since a RAC vote had already taken place on the Appendices he wanted to know whether it would require a motion to reconsider in order to get them back on the table for changes, irrespective of the status of the environmental assessment.

Dr. McGarrity said a motion to reconsider, under Robert's Rules of Order, must be made at the same meeting where the vote was taken on an issue, or the day after. However, by giving due notice, such as in the Federal Register, or by a two-thirds majority vote action to repeal, annul, or to amend, additional action could proceed. Dr. McGarrity said since this item had been published in the Federal Register, it was appropriate to be considered by the RAC.

Dr. McKinney said many of the changes made at the September 21, 1987 meeting were minor editorial changes which he would discuss with ORDA staff and he had no comments that had not been presented by previous speakers.

Dr. McGarrity said he noted some slight differences between the suggestions of USDA and the reviewers and asked that they be highlighted. He also asked that the issue of signage be reviewed, in light of Dr. Riley's comments.

Dr. Vidaver recounted that Dr. Riley preferred to have signage starting at BL2-P. She said she did not disagree with signage at any level, but that signage should be appropriate to the hazard, and that a biohazard sign was not appropriate at all levels.

Dr. Tolin said the issue of the HEPA filtration was simply an alteration which did not provide any more restriction than was already present in the NIH Guidelines, since they do not require a HEPA filter on the intake.

Dr. McGarrity then asked for a second to the motion made earlier by Dr. Vidaver that the RAC accept the proposed changes for Appendix P, as amended, to become part of the NIH Guidelines. Dr. Gellert seconded the motion.

Dr. McKinney suggested paragraph 133a be amended to say that:

> "Air filters shall be not less than 80-85% average efficiency by ASHRAE Standard 52-68 test method using atmosphere dust."

Dr. Tolin said this was a reasonable suggestion that would allow for HEPA or any other type of filter.

Mr. Manuel Barbeito, ARS, said the intent of the original suggestion was to save on the cost of installation and maintenance by prescribing a HEPA filter, thus eliminating the requirement for a 80-85 percent filter, plus a mechanical damper. This was the rationale for the alternative to the HEPA filter. He said the wording suggested by Dr. McKinney also would accomplish the intent of the suggestion.

Dr. McKinney told participants, keeping in mind the particle sizes that originate from plants, sizes of pollen and their aerodynamic characteristics, there was no precedent to require either HEPA filtration or 80-85% filtration with a back-flow damper at BL3-P if the mechanical system is designed and interlocked so the facility does not become pressurized in the event of loss of exhaust. Work with human pathogens at BL3 does not require this filtration system and there is no reason to think plant particles behave differently. The lack of consistency between BL3 and BL3-P requirements could cause confusion, in his view.

Dr. Tolin said she disagreed because there was no agreement to require equivalent containment principles for BL3 in the greenhouse and BL3 in the laboratory. The reason for the back-flow damper was to prevent passive escape of organisms when the air support fan was not pulling air into it. She said this is a common practice in greenhouses. In retrospect, she claimed, the suggestion for substituting HEPA filters instead of having both filters and dampers would be an acceptable alternative and should be approved.

There being no further discussion on the motion, Dr. McGarrity put the motion to a vote. The motion passed by a vote of 20 in favor, none opposed and two abstentions.

Dr. McGarrity then called on Dr. Vidaver to discuss the amendments to Appendix Q.

Dr. Vidaver said this would be an easier task since this was merely a codification of previously existing guidelines for animals which Dr. McGarrity had proposed at the September 21, 1987 meeting of the RAC. She said Appendix Q dealt with containment guidelines for large animals and was similar to the current biosafety levels used for small animals. The practices had been drawn from those used by USDA for many years.

Dr. Vidaver said the biosafety levels would be expressed as BL1-N through BL4-N, the "N" denoting the use of large animals, and that Appendix Q would replace the current Appendix G in the NIH Guidelines. She added that, as with plants, the majority of experiments are likely to be conducted at the lower levels of BL1-N and BL2-N.

She offered the following suggestions to amend the ARS proposal published in the December 30, 1988 issue of the Federal Register. Under Section Q-II-3-b-(g), ARS had proposed containment pens to have all perimeter joints and openings sealed to form an insect-proof structure. Dr. Vidaver suggested the last part of that sentence be revised to read "....to minimize arthropod entry and propagation," because the intent is to restrict access by mites and spiders as well as insects and to limit their multiplication. She added that at the BL1-N level structures were not "insect-proof" unless no living thing entered them.

In paragraph 233, ARS had suggested at the BL2-N level that floor drains be capped and screened. Dr. Vidaver responded that this was not consistent with containment at comparable levels for small animals and should not be required at the BL2-N level.

In paragraph 301, she noted the December 30, 1988 proposal asked for air pressure in a protective suit to be "less" than that of the adjacent area and that this was in error and it should be "greater."

Dr. Vidaver said she had a list of several typographical errors that she would provide to ORDA for correction.

Dr. Tolin said she had reviewed the ARS suggestions for consistency with previous RAC actions and found that paragraphs 34 and 184 needed to be altered to conform with a change made in the body of the NIH Guidelines at the June 3, 1988 meeting. The wording which is affected in both paragraphs is the phrase "altered by recombinant DNA techniques," and in both cases it should be changed to read "altered by stable introduction of recombinant DNA or DNA derived therefrom," to conform to the body of the NIH Guidelines.

Dr. Tolin also said she recalled in working group meetings many of the items proposed for addition to BL3-N were specifically eliminated by the working group to differentiate it from BL4-N, and that with all the additions to BL4-N it may be difficult to be able to draw a realistic separation between the two. She asked for comment from persons with more expertise in the area of animals.

Dr. Riley said she agreed with Dr. Vidaver on her suggestions dealing with arthropods and the issue of the floor drain caps at level BL2-N, but she was confused about paragraph 301 dealing with either pressure in the personnel protection suit or pressure of the room in which the suited personnel were working. She suggested elimination of the word "area" to clarify this. She said she would favor a recommendation to adopt the modifications suggested by Drs. Vidaver and Tolin.

Dr. McKinney said he agreed with Dr. Vidaver's suggestions, but he had concern over the proposed Appendix Q-II-3-b-(i). He said the proposed Appendix stated, "If a forced ventilation system is provided, the vents must be appropriately screened with 52-mesh screen." Dr. McKinney said he did not understand the intent of the word "vents," i.e., whether it was a reference to a relief vent for the forced air ventilation system or a static vent. He said he also questioned using 52-mesh screening in a BL2 facility which would require tremendous pressure within the facility and suggested this be reconsidered. Dr. McKinney believed screening was not required unless there was concern about preventing entrance when the fan was not operating.

Dr. McKinney said paragraph 261 recommended replacing the phrase "molded surgical mask or respirators," with "appropriate respiratory protection."

ARS proposed adding to paragraph 268 the phrase, "liquid waste from shower rooms and toilets may be decontaminated with chemical disinfectants by methods shown to be effective." Dr. McKinney said at BL3 in other guidelines there was no requirement to treat effluents from the facility, but simply require that contaminated waste be decontaminated. He said this suggested personnel in the facility are, in fact, contaminated and this was not really the case. He suggested if USDA personnel felt some form of treatment was necessary it should be limited to treatment of wastes originating in the facility directly housing the animal. This could be accomplished with a chemical germicide with tuberculocidal properties, rather than heat treatment which is expensive and unrealistic to ask in a facility of this nature.

Dr. McKinney said paragraph 270 proposed, "if arthropods are used in the experiment or the agent under study can be transmitted by an arthropod, the doors will be appropriately screened." He supported the use of an airlock or double airlock with an air curtain was much more effective than screening. He suggested this phrase be changed to read: "doors will be screened and additional insect control methods used;" therefore, traps and air curtains could be used to minimize entrance or exit of arthropods.

Dr. McKinney suggested changes to paragraph 271 beginning with the fourth sentence which reads:

> "The building exhaust can be used for this purpose if the exhaust air is not recirculated to any other area of the building, is discharged to the outside, and is dispersed away from occupied areas and air intakes. Personnel must verify that direction of the airflow (into the animal

room) is proper. The exhaust air from the animal room that does not pass through biological safety cabinets or other primary containment equipment can be discharged to the outside without being filtered or otherwise treated."

Dr. McKinney said this was in keeping with current practice, but the phrase "is not recirculated to any other area of the building" was redundant. Deleting this phrase would emphasize the fact exhaust is to be discharged directly outdoors. He also suggested the addition of the phrase "or the exhaust from primary containment units" be added after the word "exhaust" to produce the following new wording:

"The building exhaust, or the exhaust from primary containment units, can be used for this purpose if the exhaust air is discharged to the outside and is dispersed away from occupied areas and air intakes."

In paragraph 275, Dr. McKinney suggested the ARS additions not be accepted as they go beyond what is required for BL3 and that paragraph 271 is adequate for containment at this level.

Dr. McKinney said paragraph 308 should be changed to reflect the comments made earlier as to respiratory devices and the phrase "appropriate respiratory protection" be used.

Dr. McKinney said although USDA did not propose any changes to paragraph 317, he suggested changing the word "validate" to "monitor" which would not alter the intent but would offer the advantage of being able to use parameters such as temperature and retention time to validate the process instead of continuous monitoring with an indicator organism which would require continuous culturing before release of sewage.

Dr. McKinney said he agreed with the ARS suggestion to delete a portion of paragraph 325 referring to the NIH Laboratory Safety Monograph which is no longer available and has been superseded by other public documents.

Dr. McGarrity asked other reviewers to comment on Dr. McKinney's suggestions. Drs. Vidaver, Riley and Tolin all agreed with Dr. McKinney's suggestions. There being no other comments from the Committee, Dr. McGarrity called on Mr. Barbeito for his response.

Mr. Barbeito said that normally he would support the comments of Dr. McKinney; however he felt USDA was trying to meet the same guidelines for large animals as for laboratory containment and to be consistent with the current NIH Guidelines. He said the situation of dealing with larger animals who are shedding virus and excreting virus in feces and urine requires treatment of effluent from the containment facility. Personnel who must enter the containment area to service the animals can become contaminated. For this reason, ARS had proposed heat treatment or liquid treatment be required in paragraph 268. He said he had no quarrel with the control methods for arthropods suggested by Dr. McKinney. Mr. Barbeito stated that HEPA filtration

would be required only if the air in the containment facility was contaminated. This would be a similar function to that of biological safety cabinets, and would be consistent with other areas of the NIH Guidelines. He emphasized that large animal researchers were working in a box, that personnel had to enter the box, and that anything exiting that box, be it effluents or exhausted air, required disinfection or sterilization.

Dr. McKinney said he agreed with Mr. Barbeito as to treatment of effluents and exhaust air from animal cages, but that paragraph 268 called for treating all liquid effluents coming out of a Level 3 facility, including showers and toilets used by the investigators and laboratory staff, was more than was reasonably and scientifically required. He said, in light of doing environmental assessments, one factor to be considered is the economic impact. Dr. McKinney concluded that some balance needs to be achieved to alleviate possible challenge on the basis of asking for safeguards that are not reasonable or necessary.

Dr. McKinney added that with any aerosols likely to be generated, a single HEPA filter is all that is required because the animals are not in the open and the facility is regularly cleaned to avoid accumulations that would necessitate double filtration.

There being no other comments, Dr. McGarrity asked Dr. Vidaver to frame a motion for the Committee. Dr. Vidaver moved:

> "that the RAC accept the proposed changes for Appendix Q, as amended, to become part of the NIH Guidelines."

Dr. Atlas seconded the motion. Dr. McGarrity then called for discussion on the motion. Dr. McKinney suggested since all reviewers had written proposals, that they get together with ORDA staff to settle minor differences in language, but that paragraphs 268 and 275 still required some clarification from ARS on the issues of treatment of liquid effluents and HEPA filtration.

Mr. Barbeito was called upon to respond to Dr. McKinney's comments on these issues. He said the rationale of the shower and toilet decontamination of effluents was a precaution against inadvertent infection and was consistent with the rest of the NIH Guidelines. Dr. McKinney said a part of normal operating procedure was to issue protective clothing to laboratory workers and these would be removed before showering, thereby setting up an offsetting procedure and obviating the necessity for treatment of shower and toilet effluents. He said the procedures called for in the ARS proposal were not in line with BL3 and were essentially equivalent to BL4 in their scope.

Dr. Tolin asked about the 52-mesh screening and whether an alternative had been suggested. Mr. Barbeito said he had checked with entomologists and such screening is what is normally used. Dr. McKinney said this was the normal case for housing insects, not for working with animals. Mr. Barbeito said at BL2, it could be deleted but the intent was to prevent migration out of the facility. Dr. Tolin said that to

require it for the facility even though the test organism is not transmissible by an insect, is excessive, and that possibly a proviso could be included in the proposed wording to accommodate that. Mr. Barbeito said this was an acceptable solution.

Dr. McKinney said the final issue remaining was the HEPA filtration in paragraph 275 and the ARS suggestion that exhaust air from the BL3 animal containment zone be treated by filtering through a single HEPA filter or incinerated before release to the atmosphere. ARS called for a single HEPA filter installed on the supply side of the system and if more than 10^4 concentration of organisms were present in the air to be exhausted, dual HEPA filters would be required, one on exhaust and one on the supply, along with leak testing of exhaust ducts and filter housings, which was excessive for a BL3 facility. Dr. McKinney suggested the HEPA filtration be limited to exhaust air only and that the containment zone be treated by filtering through a single HEPA filter or equivalent. He added there were other provisions in the NIH Guidelines that deal with the issue of interlocking the supply and exhaust systems and that for BL3 facilities, there was no need for dual filtration.

Dr. Tolin agreed with Dr. McKinney. There being no further comments, Dr. McGarrity put Dr. Vidaver's motion to a vote. It passed the Committee by a vote of 20 in favor, zero against, and two abstentions.

VIII. PROPOSED ADDITION TO APPENDIX D OF THE NIH GUIDELINES:

Dr. McGarrity noted that this agenda item dealt with tabs 1345/III and 1349, and asked Dr. Clewell to begin the discussion.

Dr. Clewell said Dr. Sandra Handwerger of Beth Israel Medical Center, New York, had requested permission to clone vancomycin resistance genes from strains of Leuconostoc into the gram-positive Streptococcus sanguis strain Challis. Dr. Clewell noted that although plasmid DNA is known to be exchanged between these two species, they are not listed in the NIH Guidelines in such a way as to allow or exempt this experiment. Such experiments fall under Section III-A-3 of the NIH Guidelines which relates to "deliberate transfer of a drug-resistance trait to microorganisms that are not known to acquire it naturally if such acquisition could compromise the use of the drug to control disease agents in human or veterinary medicine or agriculture." He said this was the first time such a request had come before the RAC.

Dr. Clewell said that despite apparent reports of vancomycin-resistant strains of Streptococcus sanguis, there was some question as to the true identity of the organism and that studies at the Centers for Disease Control (CDC) suggested some isolates may have been misidentified and were actually Lactobacilli. He added that although Streptococcus sanguis is present in the normal flora of the oral cavity, it can cause serious disease such as endocarditis. Since vancomycin is frequently used as a last-resort antibiotic for such infections there was concern over using it as a host for cloning vancomycin-resistance determinants. He noted Enterococcus faecalis has already been known to have acquired vancomycin-resistance and offers a protoplast

transformation system that has already been developed. Also, he suggested that Dr. Handwerger consider certain Escherichia coli strains such as DB-11 which have altered outer membrane properties that may allow for detection of vancomycin resistance. Finally, he said it would be reasonable to attempt to use vancomycin-sensitive Leuconostoc strains that may be transformed using electrophoresis. He recommended that the RAC deny the request to clone vancomycin-resistance in Streptococcus sanguis.

Dr. Barbara Murray concurred with Dr. Clewell. She said she had talked with the CDC and they have no naturally occurring vancomycin-resistant strains of Streptococci. She noted the proposal mentioned a French experiment in which a vancomycin-resistant encoding plasmid from Enterococcus faecalis was transformed into Streptococcus sanguis, but was not a recombinant experiment and was accomplished in a laboratory and sets no precedent for meaning that such resistance has already occurred in that strain. She suggested other approaches be tried first before going ahead with this particular proposal.

Dr. Robert Murray said he was not well versed in infectious disease or problems of antibiotic resistance in patients, but that from the standpoint of safety the proposal was not warranted because such organisms, if created, could survive outside the laboratory environment and the risks outweighed the benefits.

Dr. Schaechter added that this organism is a good colonizer and requires particular care in consideration of issues of antibiotic resistance and agreed with all the reviewers.

Dr. Clewell made a motion:

> "That the RAC deny this request to clone vancomycin- resistance in Streptococcus sanguis.

Dr. Barbara Murray seconded the motion. Dr. Robert Murray asked that the investigator's letter be answered with the suggestions noted by the reviewers.

Dr. Musgrave said the applicant was present. Dr. McGarrity called on Dr. Handwerger for her comments.

Dr. Handwerger said she chose Streptococcus sanguis strain Challis because it had a lower pathogenicity than other Streptococci strains that can cause endocarditis with relative ease, whereas Challis would require a 10^3 greater inoculum to cause the disease in the rabbit model. She said the Enterococcus faecalis that was reported to be resistant was unavailable to her, although she had recently received one strain from the CDC. She said the Leuconostoc electrophoresis seemed attractive but she knew of no one who had been able to introduce genes to Leuconostoc successfully using this method.

Dr. Barbara Murray said that if one does this work in Escherichia coli, it may result in an additional level of resistance on top of the inherent resistance. Cloning into Enterococcus faecalis would be a doable experiment, in her opinion.

Dr. McGarrity said his reading of the article from the New England Journal of Medicine supplied with the proposal stated that the experiment done by the French group would not have been allowed under the NIH Guidelines.

Dr. Barbara Murray said that experiment would not have been covered by the NIH Guidelines since it was not a recombinant DNA experiment. Dr. Clewell explained that they simply took plasmid DNA from Enterococcus faecalis and transformed it into Streptococcus sanguis. Dr. Handwerger noted they later introduced it into Staphylococcus aureus by natural means and it would not colonize.

There being no further discussion, Dr. McGarrity put Dr. Clewell's motion to a vote. The motion passed by a unanimous vote of 19 in favor, none against, with no abstentions.

IX. PROPOSAL TO AMEND APPENDIX H OF THE NIH GUIDELINES:

Dr. McGarrity called on Mr. Brewer to present the proposal to amend Appendix H of the NIH Guidelines, found in tabs 1345/IV, 1350 and 1357.

As background, Mr. Brewer noted the RAC had asked the Definitions Subcommittee to work out specific language to be brought to this meeting regarding the shipment of recombinant DNA materials and etiologic agents. He noted the Subcommittee had good scientific competence and regulatory experience and that as a starting point they used the following working assumption:

> "If the Postal Service had not put out this proposed regulation, let's look at this language in light of the last 10 years and say what we know now that we didn't know then, or think we knew then, and how would we write it in light of the new information?"

Mr. Brewer said the Subcommittee recognized that even if the changes were accepted, with whatever modifications, there would be a need for cooperation and coordination with the rulemaking agencies overseeing transport and that the burden of proof was clearly on the Committee.

Mr. Brewer said there were three points he wished to make before turning the discussion over to Drs. Atlas and McKinney.

1. The Subcommittee wanted to be sure it covered plants and animals as well as cultures;

2. They wanted assurance that viral DNA was not omitted from the current definition of recombinant DNA in organisms or viruses; and

3. The Subcommittee tried to account for transgenic animals and the fact that they were not likely to survive in a double-canned, sealed shipping container.

Mr. Brewer said the Subcommittee attempted to err on the side of caution which was administratively easier than dealing with a blanket statement with numerous narrow exceptions.

Mr. Brewer said there were five corrections to make to the minutes of the meeting of the Definitions Subcommittee (Tab 1357).

1. On page 18 of the minutes, toward the end of the "Preamble:" the second line contains the phrase "appropriate requirements of the U.S. Public Health Service." The word "appropriate" should be replaced with "applicable;"

2. On page 18, same paragraph, lines 10 and 11, the words "and/or" should be replaced with the word "or;"

3. On page 18, the same paragraph, lines 9 and 10, should read: "2. Those contained in Reference G-III-2[1]," represent an attempt to cover the HIV virus. This could be accomplished by adding HIV to Appendix B which would require separate Federal Register notification;

4. The last line of the Preamble on Page 18, the word "those" is ambiguous and the phrase should be rewritten to state: "derived from those organisms or viral genomes referenced in (1), (2), and (3) above;" and

5. On page 20, the final sentence should read: "It is recommended that all organisms containing recombinant molecules which are exempt and/or Class 1 agents, should be shipped in secure, leak-proof containers."

Dr. Atlas said the problem was that changes in the U.S. Postal Service regulations were being proposed to prohibit shipping any etiologic agents via the U.S. Postal Service. The NIH Guidelines, Appendix H, stated that, "all recombinant DNA contained within organisms or viral genomes shall be shipped as etiologic agents." The sense of the Subcommittee was that not all recombinant DNA molecules contained within organisms or viral genomes were etiologic agents. In fact, only if the host organism or virus were an etiologic agent, or the source of the DNA for the

recombinant molecule came from an etiologic agent, should the recombinant organism be classified as an etiologic agent for shipment.

Dr. Atlas said the Subcommittee was surprised to find that HIV was not listed in the current NIH Guidelines as an etiologic agent and plant pathogens also were not included in Appendix B. Therefore, plant and animal pathogens listed by the Department of Agriculture were included in Appendix H.

Dr. Atlas said much time was spent both at the meeting and in phone calls afterward, trying to develop the diagram that accompanies the proposal and he agreed that the new wording, as suggested by Mr. Brewer, was satisfactory.

Dr. Erickson said perhaps the term "leak-proof" should also be expanded to include "escape-proof" for animals.

Dr. McKinney said he had nothing to add to what had been said except that part of the challenge to the Subcommittee was the fact that the CDC was also reconsidering their shipping requirements in light of the proposed Postal Service regulations. These had not been finalized and the subcommittee wanted the two agencies to be consistent on definitions of etiologic agents and shipping label requirements.

Dr. McKinney said Dr. McVicar of CDC worked closely with the Subcommittee and assured the Committee that the language relative to leak-proof containers was essentially what CDC had used. He noted the only problem may be with the degree of detail available on the CDC proposal. Some changes may occur that will require further changes in the NIH wording if action is taken on the proposal at this meeting.

Dr. McKinney suggested that if approval were granted for this proposal, ORDA staff be allowed to make minor adjustments in wording to concur with the CDC document without having to come back to the full RAC for reconsideration. He said he felt this provided the whole research world with some long overdue relief in how recombinant materials can be shipped, particularly for plants, which had to be packaged in double-walled, leak-proof containers.

Dr. McKinney said it may take up to 6 weeks for final clearance of the CDC proposal and, if they go forward with Federal Register notification, the changes could not be implemented for at least two months.

Dr. Riley suggested proceeding without any proviso regarding the new CDC version and hoped that an efficient means could be found to take it into account in the future. Dr. McKinney said he did not think it would differ significantly from the Subcommittee's proposal.

Dr. Atlas noted that CDC is not dealing with changing the definition of "recombinant organism" versus "etiologic agents," and so the substantive portion of the Preamble, as proposed by the Subcommittee, was not going to be considered by CDC. He said the

CDC submission would only affect the footnote in the Subcommittee proposal regarding shipping of non-etiologic agents.

Dr. Tolin asked if subviral genomes, sections of viruses not totally infectious but containing a recombinant clone, and plasmids with inserts, had been considered because the common feeling was that naked plasmids were exempt and required no permit for shipping. Secondly, she said she had some clarifications on the address used for the Department of Agriculture which she would give to the Subcommittee.

Dr. Pagano asked whether in the Preamble, the Subcommittee had meant strictly a "viral genome" or whether they indeed meant a "virus," in deference to not calling a "virus" an organism.

Dr. Atlas said his recollection was that the original NIH Guidelines did not cover plasmids or naked DNA being shipped as etiologic agents, but as being exempt, and that would be retained in the new definition. He said the question of "viral genome" versus "virus" did come up in the Subcommittee and the point was made that certain viral genomes potentially were infectious outside the capsid and therefore "within the viral genome" was the terminology adopted.

Dr. Pagano said that view could be challenged and that it added ambiguity to use the term "viral genome" because the infectiousness of viral genomes is a laboratory artifact.

Dr. McGarrity asked for clarification on the CDC draft. Dr. McKinney said as a result of the hearings held by the U.S. Postal Service, CDC was charged with going back and updating 42 CFR Part 72, which covered regulations promulgated by the Public Health Service that are in for prepublication clearance. There is the possibility that some language in the revised 42 CFR might lead to minor adjustments in the recommendations of the Definitions Subcommittee.

Mr. Brewer said the remaining change was the diagram and not the definitions.

Dr. Clewell asked if the phrase "...those listed as Class 2, 3, or 4 agents in Appendix B," should not be listed as "Class 2, 3, or 4 agents." Mr. Brewer said they should be so listed. Dr. Clewell added that the phrase in item 3, "those regulated as animal or plant pathogens or pests," should not be changed to read "those regulated by virtue of their coming from animal or plant pathogens or pests."

Dr. McKinney said the origin of the sequences is not what causes them to be shipped as etiologic agents but what is being expressed. He said it was possible to get a sequence out of a Class 4 agent and put it into Escherichia coli K-12, and, as long as it was a benign sequence and did not express any pathogenic characteristics, it would not have to be shipped as an etiologic agent.

Dr. Joe Van Houten of Schering-Plough Corporation said that item 4 troubled him because it states that if material is taken from a host organism that is pathogenic and

it is placed into another host, then that host is automatically considered an etiologic agent. He gave as an example, Saccharomyces cerevisae containing a surface antigen from hepatitis B virus, and asked whether it was intended that such an agent should be viewed as an etiologic agent. Further, he said the way the document was written, mammalian cell cultures would now be considered etiologic agents if they contain a piece of a pathogen but had not been so considered in the past.

Dr. Atlas said Dr. Van Houten was correct and that clearly this was over-restrictive. However, the Subcommittee had dealt with this issue for some time and felt that to define by coding regions coding for pathogenicity was creating more problems than the Subcommittee was solving, in reference to shipping. He added that Dr. Stevenson, American Type Culture Collection, was on the Subcommittee and said this proposal would cause minimal problems in shipping. To go through the regulatory process of trying to get exemptions based on pathogenicity was more difficult than just putting the right labels on them and shipping them as etiologic agents. Dr. Atlas noted that overall, there would be a reduction in items shipped as etiologic agents because at the present time any agent containing a recombinant molecule has to be shipped as an etiologic agent.

Dr. Van Houten asked about the issue of commercial transfers of large fermentation products from one plant to another. He said that under the guidelines being proposed, a 10-liter fermentation vessel would have to be broken down into 500-milliliter aliquots and then shipped with no more than 8 liters per shipping container. This would be somewhat inconvenient for an agent that is not considered as either pathogenic or etiologic.

Dr. Tolin said she saw no reference in either the minutes or the discussion of the recent ruling from APHIS with regard to shipment of plant pathogens. These are covered under the April 20, 1987 revision of 7 CFR 340, in which the requirement for permits of certain clones from plant pathogens were specifically eliminated on the basis that certain sequences were not involved with pathogenicity and did not require permits under the Plant Pest Act. She added that it had been published in the Federal Register and is germane to the discussion.

Dr. Tolin said 7 CFR 340 is the final rule regarding recombinant DNA and plant pathogens, specifically host-vector systems, and may set a precedent for not having to declare organisms with benign sequences from being labeled as pathogens or etiologic agents.

Dr. Riley said some effort should be made to distinguish between cloned portions of an etiologic agent that carry a degree of hazard and those that do not. Any amendment to Appendix H should be made on firm scientific grounds.

Dr. Henry Miller, Food and Drug Administration liaison to the RAC, urged that wording be developed that would enable small, benign portions of pathogens going into non-pathogens not to be classified as etiologic agents. He said this situation had provided problems in a field release where a Rhizobium could not be field tested

because it contained a very small piece of a plasmid from a pathogen and fell into EPA's regulatory net. He said the "Coordinated Framework for Regulation of Biotechnology" published in 1986 stated that the incorporation of well-characterized non-coding regulatory sequences into a non-pathogen did not automatically confer pathogenicity on the recipient.

He said this was analogous to a self-cloning manipulation and it might be possible to use this kind of language in the proposal, although it would not solve the objections of Dr. Van Houten.

Dr. McKinney said the issue of large volume shipments was not a new one, but that it was impossible for the Subcommittee to concern itself with shipping a fermenter full of liquid. He said there were safe ways of doing this that did not require packaging as an etiologic agent. He agreed with Dr. Miller's suggestion and asked if there was further suggestion for wording so that well-characterized non-coding sequences in a non-pathogen could be accommodated.

Mr. Brewer said the Subcommittee had studied the proposed regulations being promulgated by both the Department of Transportation (DOT) and USDA and that the language proposed in the amendment to Appendix H which states "those coming from animals or plant pathogens or pests under Title 7," would cover such circumstances if they were not further defined under Title 7.

Dr. Tolin agreed and noted the actions being taken under Title 7 would allow for shipment of sequences from pathogens if they are known to have no relation to pathogenicity without labeling as a pathogen, and that etiologic agents could be viewed in the same manner.

Mr. Brewer said the proposal was the best that could be put together given the time constraints placed upon the Subcommittee and that they would be happy to reconsider the matter in light of the feedback from this meeting.

Dr. Riley asked if the wording suggested by Dr. Tolin could be adopted and thereby solve the problem. Dr. John Payne of the USDA said he was the principal writer of the exclusions from the USDA regulations. He said the exclusions they sought were in line with exclusions in the NIH Guidelines. He said the intent of the USDA exclusions was to mirror the NIH Guidelines as closely as possible and that now it seemed more restrictive language was being sought for the NIH Guidelines.

Dr. Tolin said the basis for the change in the USDA regulations was that the Appendix H of the NIH Guidelines considered sequences in bacteria as exempt organisms and not covered under Appendix H.

Dr. Gellert moved that the RAC refer the matter back to the Subcommittee on Definitions for more work and to take into consideration all comments made at this meeting. Mr. Brewer seconded the motion.

There being no further comment on the matter, Dr. McGarrity put the motion to a vote. The motion passed by a vote of 14 in favor, none opposed and one abstention. Dr. McGarrity thanked the Committee for its comments and thanked Mr. Brewer and the Definitions Subcommittee for their work. He then asked to move to the next agenda item.

X. PROPOSAL TO AMEND SECTION I-B OF THE NIH GUIDELINES:

Dr. McGarrity drew the Committee's attention to tabs 1345/VII and 1353 which pertained to this agenda item and called on Dr. Gellert to begin the discussion.

Dr. Gellert said a proposal had come from the National Wildlife Federation suggesting that new methods of introducing DNA into organisms without prior construction of a recombinant be covered under an expanded set of Guidelines. He said this covered experiments such as transfer of naturally occurring drug resistance traits to an organism where they are not normally found, as well as the introduction of a retroviral gene into a transgenic animal by the direct insertion of a viral core.

Dr. Gellert said it was important to consider which experiments were practical at present and to draw a distinction between experiments done on a cellular level versus the whole animal or plant level. He added that it would be rather difficult to write one broad set of guidelines covering all possibilities in a rational way and that many such experiments may not present hazards. He suggested the matter be sent to a subcommittee to consider which subcategories of experiments should be included in the purview of the RAC and that an extremely broad set of guidelines not be written which would require the RAC to later consider numerous exclusions.

Dr. Riley said the National Wildlife Federation had made a valid point, that the technology has expanded. There are now various methods by which recombinant DNAs can be generated and that it is not the methodology that is important, but the characteristics of the product and whether the product is hazardous.

She said she agreed with Dr. Gellert that it would not be easy to expand the definition of "recombinant DNA" without making the definition so broad as to be unworkable, and said it was a task requiring more work than could be done around the table at a RAC meeting.

Dr. McGarrity noted that there was a Subcommittee on Revisions of the Guidelines, which would be the appropriate group to which to refer this matter.

Dr. Roberts said the National Wildlife Federation letter led him to believe there was a new technology that superseded recombinant DNA, but that many of the techniques described as new had been used all along in recombinant DNA research and this was not as dramatic a shift as reflected in the letter. He added that it was hard to conceive of a way any of the technologies for introducing DNA into cells could produce anything unless one begins with an extracted and inevitably recombinant

DNA in the first place and that further regulation seemed to be pointless. However, he said it was something the Committee should be thinking about.

Dr. Bourquin underlined Dr. Riley's concern that the product is really the issue, rather than the technique for producing it and added he was reluctant to expand the definition of "recombinant DNA" as it could cause the RAC to become bogged down with every experiment using recombined or altered organisms. He suggested additional work looking at how to expand the definition while limiting it so as to make it a workable definition.

Dr. Schaechter said he agreed with all the comments made. On one hand he had sympathy for expanding the definition, but that in light of history, a blanket definition would only cause the RAC to have to create exclusions to the definition. He noted that Dr. Gellert had mentioned "rational experiments," and Dr. Schaechter said "irrational experiments" also had to be taken into account so that certain projects didn't fall through cracks in the NIH Guidelines.

Dr. Murray said that the issue discussed previously at the meeting dealing with the vancomycin-resistance experiments was deemed hazardous by at least two reviewers and was an example of loopholes in the NIH Guidelines that needed to be covered. He added that it may be appropriate to send this matter to a subcommittee. However, he proposed that ORDA staff members consider consulting experts in the field to prepare a paper reviewing the current literature in the field to help determine whether additional guidelines are necessary and at the same time allow the subcommittee to work on the matter and bring a recommendation back to the full Committee.

Dr. McGarrity said he thought a review of the literature was an administrative function that could be undertaken by ORDA staff with consultation from appropriate members of the RAC.

Dr. Miller said the comments made echoed those of the National Academy of Sciences' White Paper published in 1986. One of their conclusions was that risks associated with recombinant DNA engineered organisms are the same as those associated with unmodified organisms and organisms modified by other methods. This showed there should be a product-based approach to oversight and not a process-based approach. He noted that the NIH Guidelines had always been process-based, encompassing only recombinant DNA, and that in the past, members of the RAC had resolved this issue by limiting their jurisdiction only to applications felt to be unique in some way. He said they did not adopt a risk-based approach, but limited their jurisdiction to experiments not covered by other Federal agencies.

Dr. Miller said there were cases where organisms that are not benign can be manipulated by cell cloning, whose risk is non-trivial, or in which the wild type is manipulated by self-cloning, and this needs to be carefully considered. He said the point was that there appeared to be a dichotomy of review, with other Federal

agencies stringently overseeing field trials, while laboratory research is overseen under the NIH and CDC Guidelines.

Dr. Miller added that laboratory research, whether with recombinant organisms or not, does get oversight and operates effectively and the question of increased jurisdiction is not one which the subcommittee should consider, but that areas not adequately covered by Federal agencies need to be delineated.

Ms. Margaret Mellon of the National Wildlife Federation said she was pleased the RAC was considering referring the issue to a subcommittee and wanted to add a few additional points in response to the Committee's comments.

Ms. Mellon said expansion of the scope of the NIH Guidelines did not necessarily mean a lot of additional activities were going to be receiving heavy regulation because the nature of the NIH Guidelines is to cast a broad net for types of activities and organisms, but within that net, to leave most projects under a light regulatory burden. She said if the scope of the NIH Guidelines were enlarged, she expected most of the newly regulated organisms would fall in the lightly-regulated categories.

She pointed out that the NIH Guidelines have more importance than Dr. Miller had suggested in his remarks in that other Federal agencies, as well as foreign governments and international agencies, have adopted them as they stand. Therefore, Dr. Mellon concluded, it is important to take into account progress in the field in devising any new definition because it will have widespread ramifications.

Dr. McKinney said he understood why the proposal had been submitted, but that a change in the definition of "recombinant DNA" would cause other portions of the NIH Guidelines to have to be reviewed against the new definition. He stated that it was important to realize that it will be difficult to devise a new definition to take future technologies into account in which little is known of their potential associated risks. Dr. McKinney cautioned the Committee to give long, deliberate consideration to any change in the definition before putting into place new language that may or may not be desirable.

Dr. Miller said he agreed with Dr. McKinney as to the difficulty of the task but he felt what was needed was a definition that would take into account the potential hazard, not genetic novelty, of an organism.

Ms. Mellon said she would agree if the NIH Guidelines were product-based, but since they are purely process-based, new processes and a list of available techniques should be added. Dr. Bourquin asked how much of what was being discussed in terms of developing organisms was covered by other mechanisms such as other committees and local Institutional Biosafety Committees (IBCs) that wouldn't have to be reviewed by the RAC. Dr. McGarrity said his opinion was that there were inconsistent standards that differ with each IBC. Dr. Miller added that it depended on whether deliberate release or scale-up experiments were being discussed.

Dr. Murray said at his institution, the Biohazards Committee had been expanded to include any biological organism posing a hazard. This included recombinant DNA but was not limited to recombinant DNA. He said other institutions' committees do not review anything unless it is recombinant DNA.

Mr. Mannix said there was a danger of being far too expansive in viewing this as an exercise in closing loopholes and trying to include every organism that has a hazard associated with it. In this light, wild type organisms would dominate every other possible source of hazardous organisms. He said no scientist has ever come up with any organism as violent as nature has produced and that he felt it was not the role of the Committee to apply the NIH Guidelines to naturally occurring organisms.

Dr. McGarrity noted that the Committee was down to a bare quorum and that he would entertain a motion on the topic. Dr. Riley moved the matter be referred to the Subcommittee on Revision of the Guidelines. Dr. Murray seconded the motion.

There being no further discussion, Dr. McGarrity put the motion to a vote. The motion passed unanimously.

XI. FUTURE MEETING DATES:

Dr. McGarrity noted the next meeting of the RAC will be June 5, 1989, and that future meetings will be on October 6, 1989, February 5, 1990, and June 1, 1990.

Having concluded the agenda and there being no further business to be discussed, Dr. McGarrity adjourned the Committee at 4:35 p.m., on January 30, 1989.

Jay Moskowitz, Ph.D.
Acting Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

Date: 10/6/89

Gerard J. McGarrity, Ph.D.
Chairman
Recombinant DNA Advisory Committee
National Institutes of Health